1990

ANNUAL REPORT

MANITOBA CANCER TREATMENT
AND RESEARCH FOUNDATION

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1990 ANNUAL REPORT
Manitoba Cancer Treatment and Research Foundation
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REPORT OF THE CHAIRMAN

The Honourable Donald W. Orchard
Minister of Health.

Dear Mr. Orchard:

I have the honour of forwarding this report for the year 1990/91 on behalf of the Manitoba Cancer Treatment and Research Foundation.

As the number of cancer patients within the Province and the number of referrals to the Foundation increase, the facilities of the Foundation are stretched ever more and we are indebted to an excellent staff, whose dedication to patient care continues to encompass this increasing load. The planning process for the expanded cancer treatment facility at its Olivia Street location is now well underway. The staff, in addition to carrying out their usual duties, have been exemplary in their contribution towards this planning process. The building program is made possible by joint public subscription and Government funding and the public response to the need has been most encouraging and is an indication both of the need and of the support which the Foundation has amongst Manitobans.

The year has been marked by the completion of the installation of two linear accelerators, which are essential components of maintaining state-of-the art therapy for these patients. The bone marrow transplant program which is carried out in conjunction with Health Sciences Centre was initiated and represents a major advance, not only in treatment but in convenience for Manitobans who no longer must leave the Province for this procedure. The Outreach Program of the Foundation which extends chemotherapy beyond the urban boundaries continues to expand and to provide services at a distance from the Foundation.

I would again like to extend my personal thanks to the staff of the Foundation for their dedication to patient care and the purposes of the Foundation.

Yours truly,

D.J. McMullin, C.A.
Chairman

ORGANIZATION

THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

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G.V. Krepart, B.Sc., M.D., FRCSC, VACM(Ob/Gyn), FGO, SBCGO
L.G. Israels, B.A., M.D., M.Sc., FRCPC
I.C. Peever, M.D., FACOG, FSOGO, FRCSC
B. Weinerman, M.D., FRCPC

Scientific Advisory Committee

H. Duckworth, B.Sc., Ph.D.
Professor, Dept. of Chemistry
University of Manitoba

A. Froese, B.Sc., Ph.D.
Professor, Dept. of Immunology
University of Manitoba

F. Labella, B.A., M.A., Ph.D.
Professor, Dept. of Pharmacology and Therapeutics
University of Manitoba

Ex Officio

L. G. Israels, B.A., M.D., M.Sc., FRCPC
Executive Director
Manitoba Cancer Treatment & Research Foundation

Administration

Executive Director - L. G. Israels, B.A., M.D., M.Sc., FRCPC
Assistant Executive Director - R. R. Publow (to June 1990)
Director of Finance - A.E. Joseph, C.A. (effective June 1990)
Director of Human Resources - G. Hanson (effective June 1990)
Executive Secretary - J. Morton
Administrative Assistant Finance - I. Birse
Administrative Assistant Personnel - L. Walesiak
Accounts Payable - M. Gemmell

Professional Staff

The Foundation is an integral part of the teaching and research program of the University of Manitoba. Various staff members participate in the undergraduate oncology program, teach on the hospital wards, and have graduate students in their laboratories.

UNIVERSITY APPOINTMENTS

Faculty of Medicine

Department Of Anatomy
Dr. G. Froese, *Associate Professor*

Department of Biochemistry
Dr. J. Wright, *Professor*
Dr. L.G. Israels, *Adjunct Professor*

Department Of Human Genetics
Dr. A.H. Greenberg, *Professor*

Department of Immunology
- Dr. F. Paraskevas, *Professor*
- Dr. A. Greenberg, *Professor*
- Dr. D.A. Chow, *Assistant Professor*

Department of Internal Medicine
- Dr. L.G. Israels, *Distinguished Professor*
- Dr. E. Baral, *Professor*
- Dr. D. Bowman, *Professor*
- Dr. G.J. Goldenberg, *Professor*
- Dr. F. Paraskevas, *Professor*
- Dr. B. Schacter, *Professor*
- Dr. B. Weinerman, *Professor*
- Dr. L. Brandes, *Associate Professor*
- Dr. M. Levitt, *Associate Professor*
- Dr. H. Schipper, *Associate Professor*
- Dr. A. Begleiter, *Assistant Professor*
- Dr. E. Bow, *Assistant Professor*
- Dr. J. Johnston, *Assistant Professor*
- Dr. H.Y.P. Lam, *Assistant Professor*
- Dr. T. Shore, *Assistant Professor*
- Dr. J. Wright, *Adjunct Professor*

Department of Obstetrics and Gynecology
- Dr. G.V. Krepart, *Professor*
- Dr. R.J. Lotocki, *Assistant Professor*

Department of Pediatrics
- Dr. A. Bishop, *Professor*
- Dr. A.H. Greenberg, *Professor*
- Dr. J.M. Gerrard, *Associate Professor*
- Dr. E.D. Israels, *Associate Professor*
- Dr. M. Schroeder, *Associate Professor*
- Dr. S.J. Israels, *Assistant Professor*

Department of Physiology
- Dr. J. Dodd, *Assistant Professor*
- Dr. M. Mowat, *Assistant Professor*
- Dr. A.H. Greenberg, *Adjunct Professor*

Department of Radiology
- Dr. E. Baral, *Professor*
- Dr. S. Shalev, *Associate Professor*
- Dr. P. Dunscombe, *Assistant Professor*
- Dr. S. El Sayed, *Assistant Professor*
- Dr. G. Froese, *Assistant Professor*
- Dr. P. Hahn, *Assistant Professor*
- Dr. W. Huda, *Assistant Professor*
- Dr. K.D. Jones, *Assistant Professor*
- Dr. W. McLellan, *Assistant Professor*

Department of Radiology (cont'd)
- Dr. R.E. Palser, *Assistant Professor*
- Dr. A. Sourkes, *Assistant Professor*
- Dr. E. Hadzic, *Lecturer*
- Dr. S. Larsson, *Lecturer*
- Dr. K. Vijayaraghavan, *Lecturer*

Department of Surgery
- Dr. E. Ramsey, *Professor*
- Dr. W. Beecroft, *Associate Professor*
- Dr. B. J. Anderson, *Assistant Professor*

Department of Social and Preventive Medicine
- Dr. N.W. Choi, *Professor*
- Dr. N.A. Nelson, *Associate Professor*
- Mrs. P.F. Moodie, *Lecturer*

Faculty of Science

Department of Microbiology
- Dr. J. Wright, *Professor*

Department of Physics
- Dr. J. Bews, *Adjunct Professor*
- Dr. P. Dunscombe, *Adjunct Professor*
- Dr. G. Froese, *Adjunct Professor*
- Dr. W. Huda, *Adjunct Professor*
- Dr. R. Palser, *Adjunct Professor*
- Dr. S. Shalev, *Adjunct Professor*
- Dr. A. Sourkes, *Adjunct Professor*
- Dr. D. Viggars, *Adjunct Professor*

Computer Science
- Dr. D. Scuse, *Professor*

Department Heads

Clinical Programs
  Brent Schacter, M.D., FRCPC

Epidemiology and Biostatistics
  Nung Won Choi, M.D., M.P.H., Ph.D., FACE

Finance
  Aaron E. Joseph, C.A.

Gynecological Oncology
  Garry Krepart, M.D., B.Sc.(Med), FRCSC, FACOG

Hematology Laboratory
  Susan Tighe, R.T.

Human Resources
  Gloria Hanson

Information Services
  Harvey Schipper, B.A.Sc., M.D., FRCPC
  Peter West

Library
  Donna Chornenki

Manitoba Institute of Cell Biology
  A. Greenberg, M.D., Ph.D.

Medical Oncology
  MacCharles Unit - David M. Bowman, M.D., B.Sc.(Med), FRCPC
  St. Boniface Unit - Harvey Schipper, B.A.Sc., M.D., FRCPC

Medical Physics
  Peter Dunscombe, Ph.D., FCCPM
  Shlomo Shalev, Ph.D.

Nursing
  Beverley Glenday, R.N.
  Barbara Warren, R.N., M.S.N.

Outreach
  Harvey Schipper, B.A.Sc., M.D., FRCPC
  Anne Nemecek, R.N., P.H.N.

Pediatric Hematology/Oncology
  Jon Gerrard, M.D., Ph.D., FRCPC

Pharmacy
  Venetia Bourrier, B.Sc.(Pharm).

Psychiatric Oncology Service
  Harvey Chochinov, M.D., FRCPC

Radiation Oncology
    Edward Baral, M.D., Ph.D.

Radiotherapy Treatment Floor
    Joan Howes, R.T.T.

Radiation Therapy Techonolgist Training Program
    Elvera Kirk, R.N., A.C.T., C.A.E.

Records and Registry
    Harvey Schipper, B.A.Sc., M.D., FRCPC
    Gloria Hanson, CCHRA(A)

Social Work
    Betty Wong, M.S.W., R.S.W.

Surgical Oncology
    Wayne Beecroft, D.D.S., M.D., FRCPC, FACS
    Barry Anderson, M.D., FRCSC

Urologic Oncology
    Ernest Ramsay, M.B., B.Ch., FRCPC

Volunteer Services
    Elaine Hickerson, B.A.

Volunteer Services - Canadian Cancer Society
    Helen Morrow

MANITOBA INSTITUTE OF CELL BIOLOGY

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J. Jamieson, *Head, Department of Chemistry, University of Manitoba*
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Ex Officio
A. Greenberg

DEPARTMENTS

EPIDEMIOLOGY AND BIOSTATISTICS

Nung Won Choi, M.D., M.P.H., Ph.D., F.A.C.E., *Director*
Marie-Paule Regan, *Secretary*

Scientific Staff

Norma A. Nelson, Ph.D., *Biostatistician*
Patricia F. Moodie, M.A., *Biostatistician*

Postdoctoral Fellow

Pei-Zhong Wang, M.D., M.P.H.

Data Processing

Marie-Paule Regan

Research Assistants

Jeannine Du
Janet Ediger

Field Investigators

Linda Archer
Shirley Cormack
Shirley Elgert
Chris Sobie
Johanna Stasiuk
Christine Strutt
Janis Wolfe

Support Clerks

Audrey Glidden
Jill Redden

Awards and Honours

Consultant, Western Pacific Regional Office of the World Health Organization on Non-Communicable Disease Control, Manila, Philippines, March-May, 1990.

Post-Doctoral Awards

Pei-Zhong Wang, Tianjin Medical College, People's Republic of China. University of Manitoba/Health and Welfare Canada

The scope of the departmental research programme consists of descriptive and analytical epidemiological studies on cancer among certain ethnic groups, immigrants and their descendants, native populations and populations residing in remote areas of the province as well as environmental and industrial impact on urban and rural communities.

The discipline of Epidemiology is a branch of medical science which studies distributions, determinants and natural histories of diseases such as cancer, in a community.

Our department has a longstanding (for more than 20 years) interaction with the Manitoba Cancer Registry which is our primary source for epidemiological studies and is one of the better registries in the world.

One of the department's activities is to give consultation to other departments of the Foundation as well as to other researchers in the province. Requests are received from many agencies and individuals including government agencies for data analyses and statistical epidemiological investigations.

The ongoing projects are as follows:

Epidemiology

1. Case-control study of lung cancer and radon exposure.
2. Childhood leukemia and low frequency electromagnetic field exposure.
3. Case-control study of pesticide use and health.
4. International study of brain tumours among adults: a case-control study.
5. International study of brain tumours among children: a case-control study.
6. Western Provinces Cancer Mapping Project.

Biostatistics

In addition to providing the statistical analyses and programming for the major projects in our department as outlined in this report, we provided consultation on research design, statistical analysis and programming for researchers in the other departments in the Foundation.

Our section was involved in the Residency Teaching Programme of the Radiation Oncology Department at the Foundation.

The Director of the department has been engaged in international collaborative studies as well as doing consulting work with the World Health Organization on cancer prevention and control.

The staff of the department has been involved in undergraduate, graduate and residency educational programmes in epidemiology and biostatistics at the University of Manitoba involving the Community Health Sciences Department.

The department has fully participated in research, consultation and educational programmes of the Foundation.

Research Report

These research projects were made possible with the support of the Manitoba Cancer Treatment and Research Foundation, the Manitoba Medical Services Foundation and the Manitoba Helath Services Commission and the collaboration of governments of the Province of Manitoba and the City of Winnipeg. We have also received support from and collaborated with the National Cancer Institute of Canada Epidemiology Unit, Medical Services Bureau of Health and Welfare Canada, many Canadian universities and the International Agency for Research on Cancer, Lyon, France.

We would particularly like to acknowledge the support we received from the Bureau of Radiation and Medical Devices of Health and Welfare Canada and its Environmental Health Directorate for the Lung Cancer and Radon Exposure Study. This has been a six year project that will be completed in March of 1992.

CASE- CONTROL STUDY OF LUNG CANCER AND EXPOSURE TO RADON AND RADON DAUGHTERS

Phase I

N.W. Choi, N.A. Nelson, P.F. Moodie, J. Du, C. Sobie, C. Strutt, J. Stasiuk, M-P. Regan, H.C. Oh, P-Z. Wang

As presented in last year's report, this phase of the study has been completed July of 1990. Our goal of interviewing 750 lung cancer cases and 750 controls (matched by sex and age +5) has been reached. Data have been sent to the Environmental Health Directorate in Ottawa for analysis, and we have been analyzing certain aspects of the study independently. The findings should prove interesting as the questionnaire contained questions on previous residence since birth, occupations and exposure to occupational substances, smoking as well as passive smoking history, medical history and radon testing. Epidemiologists in North America and Europe have recognized the importance of radon gas as a potential agent for risk (added/interactive) of lung cancer.

This is the largest study of its kind ever conducted.

Preliminary findings should be available in 1991.

Phase II

N.W. Choi, N.A. Nelson, J. Du, S. Cormack, L. Archer, S. Elgert, J. Wolfe, A. Glidden, J. Redden, M-P. Regan

The object of Phase II of the Lung Cancer Study is to try to get a lifetime reading of radon exposure for each case and control interviewed in Phase I. Each subject was questioned on all his/her previous residences. Occupants of these homes were then contacted, and with their consent, dosimeters were left in the house for two six month periods.

This phase of the study is progressing well and should be completed by March 1992.

EPIDEMIOLOGIC STUDY OF CHILDHOOD LEUKEMIA AND LOW FREQUENCY ELECTROMAGNETIC FIELDS

N.W. Choi, J. Gerrard, M. McBride, J. Ediger, M-P. Regan, K. Hjalmarsson

Recent studies have suggested that children exposed to strong low frequency electrical or magnetic fields (EMF) may be at higher risks of leukemia. Two limitations of these studies were the inability to accurately quantify electromagnetic exposure and an insufficient number of leukemia cases to adequately measure any relationship among different types of leukemia.

Use of a new electromagnetic field dosimeter (Positron Model 37810) developed in Canada will allow for assessment of exposure with far greater accuracy and consistency than in any previous study. Indirect exposure assessment will be by observation of wiring configurations in current and previous residences.

Participation by 7 study centres across Canada should allow accrual of enough cases to investigate the putative association among leukemia subtypes if any.

It should be emphasized that EMF is only one of the factors to be examined. A number of other potentially causative and confounding factors will also be examined in a personal interview.

A pilot study conducted in the Vancouver area from March 1990 to September 1990 has demonstrated that personal dosimetry of children is feasible. Level of compliance of subjects was virtually 100%. Procedures for EMF assessment using wiring configuration codes have been tested. Procedures for data collection in the study have been developed, tested and documented. These procedures have been reviewed with all provincial centres and data quality control measures incorporated.

Training of study personnel has taken place and interviews of subjects will start March 1991.

WESTERN PROVINCES CANCER MAPPING PROJECT

H. Berkel, P. Band, N.W. Choi, W.A. Anderson, J. Ediger, P. West, G. Hanson/H. Whittaker, M-P. Regan

A project of cancer mapping is being proposed by the Alberta Cancer Board for the four western provinces and the Manitoba team has decided to collaborate as the topic has been of great interest to us.

The objective of the study is to examine cancer incidence by geographic distribution in the four western provinces in Canada. Observed patterns and/or differences in cancer incidence by region will provide the basis for hypothesis generation, hypotheses that are to be further examined in analytical studies. The resulting analytical epidemiological research studies would be aimed at investigating environmental and/or occupational factors that might be preventable.

In addition, the cancer atlas resulting from this study may provide answers to concerns about possible existing clusters of cancer in certain areas. Finally, the atlas could be used to assess the need for cancer care services on a regional basis in the provinces.

CASE-CONTROL STUDY OF PESTICIDE USE AND HEALTH

N.W. Choi, J. Dosman, H.H. McDuffie, J. Ediger

The purpose of the study is to determine the relationship between the incidence of certain types of cancers and exposure to pesticides in four regions of Canada (the Prairies, Ontario, Quebec and the Maritimes).

The cases will be males 19 years and older who have been diagnosed with soft tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma or multiple myeloma; controls will be matched for sex and age.

All subjects will initially be sent a mail-in questionnaire to obtain information on pesticide exposure, demographics, geographical locations, occupations and behavioural factors. Those subjects who indicate pesticide exposure will be mailed the detailed pesticide list, questionnaire and a telephone interview will be conducted.

The pilot study phase of this project has been successfully completed and the finalization of procedures is taking place. The interviewing phase of the study will begin July, 1991.

COLLABORATION ON STUDY OF CANCER INCIDENCE IN REGISTERED NATIVE INDIANS IN ONTARIO

L. Marrett, N.W. Choi, J. Ediger, G.Hanson/H. Whittaker, M-P. Regan

Our department will be participating in a project in collaboration with the Ontario Cancer Treatment and Research Foundation regarding their linkage of the registered native Indians of Ontario to their Cancer Registry for the period 1966-1983.

It has been proposed that we collaborate on this project as many Ontario natives reside in the far northwest corner of the Province of Ontario and come to Winnipeg for cancer treatment. They may, therefore, never be recorded in the Ontario Cancer Registry. There are about 17,000 to 18,000 natives who could come to our province for cancer care.

We have done similar work last year linking registered native Indians of Manitoba to our cancer registry. (see 1989 annual report).

Special Requests

During 1990 our department was asked to provide various statistical investigations on cancer occurrence in the province by many governmental agencies and the private sector. These requests involve special calculations using in-house computer programs for detecting possibly unusual occurrences of cancer(s).

Biostatistics Research Activities

N.A. Nelson, P.F. Moodie

As part of the statistical consultations given by the biostatisticians, the effects of chemotherapy as an adjuvant treatment for certain cancers have been studied. Meta analysis (summarizing results from reported studies) is being used in a current project where the effect of adjuvant chemotherapy on survival and side effects have been reported from randomized clinical trials. Twenty four trials, where sufficient survival analyses were reported for inclusion in a summary, consisted of 3,343 individual patients. Considerable power for drawing conclusions would exist if each trial were reported with the expectation that it would become part of a meta analysis. The survival statistics for the individual trials were often appropriately reported as conclusions drawn from log rank tests and acturial or product limit survival estimates (these estimates were not always accompanied by estimates of standard error). However, with standards for stratification before randomization, reporting of the observed and expected values as well as the denominators of the log rank test for each strata and with estimates of relative hazards one could make the best possible use of the experience of the more than 3000 patients. Treatment effects and the interaction of these effects with the strata as well as with variations in treatment protocol could then be efficiently estimated.

Publications

Kaldor, J.M., Day, N.E., Choi, N.W. and IARC Working Group. Leukemia Following Chemotherapy for Ovarian Cancer. N. Engl. J. Med. 322: 1-6, 1990

Kaldor, J.M., Day, N.E., Choi, N.W. and IARC Working Group. Leukemia Following Hodgkin's Disease.N. Engl. J. Med. 322: 7-13, 1990

L'Abbe, K.A., Howe, G.R., Burch, J.D., Miller, A.B., Abbatt, J., Band ,P., Choi, N.W., Du, J., et al. Radon Exposure, Cigarette Smoking and Other Mining Experience in the Beaverlodge Uranium Miners Cohort. Health Physics (in press), 1991.

Hill, G., Choi, N.W., and the CCRERG Working Group. Case-Control Study of Thyroid Cancer with Emphasis on Radiation as a Risk Factor.CMAJ (in press), 1991.

GYNECOLOGIC ONCOLOGY

Garry V. Krepart, M.D., B.Sc.(Med.), FRCSC, FACOG, *Section Head*

Section Members

Robert Lotocki,. M.D., B.Sc., FRCSC, FACOG
Mark Heywood, M.D., FRCSC

Clinical Fellows

Michael Fung Kee Fung, M.D., FRCSC

Residents

S. Gader, M.D. B.Sc. (Trop. Med.)
T. Kosalka, M.D.
R. Ke, M.D., B.Sc.(Biol.)
S. Taylor, M.D.

Organization

The Section of Gynecologic Oncology is represented at the Manitoba Cancer Treatment and Research Foundation as well as at the St. Boniface Oncology Unit at the Health Sciences Centre and St. Boniface General Hospital. Members belong to the Section of Gynecologic Oncology of the Department of Obstetrics, Gynecology and Reproductive Sciences of the Faculty of Medicine. Clinics are held four one-half days weekly at the Manitoba Cancer Treatment and Research Foundation and two half days at the St. Boniface Oncology Unit. Colposcopy clinics at St. Boniface Hospital are scheduled four half days a week. Close liaison is maintained with the Radiotherapy and Medical Oncology Divisions as well as with urologic and surgical oncologists at both institutions. Referred patients are seen at both Oncology units and appropriate consultations, if needed, with other divisions. Hospital admissions are at the Women's Hospital or at St. Boniface Hospital. An Oncology Unit as well as a high-dependency area and a dedicated inpatient chemotherapy nurse are available at the Women's Hospital with similar facilities at St. Boniface Hospital on the Gynecology Service.

Teaching

Various levels of teaching are offered by the Gynecologic Oncology Service. A two-year postgraduate Fellowship Program was established in 1981. The Royal College of Physicians and Surgeons of Canada has recognized Manitoba as one of three training centres in Canada for Gyne-Oncology, now recognized as a sub-specialty by the College. Currently the Program has one Fellow, Dr. M. Fung Kee Fung, graduating in June of 1991. Dr. M. Heywood, a previous Fellow, joined Bob Lotocki and Garry Krepart to bring the compliment of the Division to three full time members. Residents in their third and fourth year of Ob/Gyn rotate for 3 months through the Section as part of their training, as well as Medical Oncology and Radiation Oncology residents. Tumour Conferences are held weekly at the Women's Hospital and St. Boniface Hospital with much appreciated pathology backup by Dr. M. Paraskevas and by Dr. G. Vadas. Reviews of current subjects in Gynecologic Oncology or pertinent clinical cases are presented for all residents, medical students, interns and staff.

The Section is responsible for chemotherapy as well as surgery. Bowel as well as urinary complications are handled at both teaching hospitals. Full support is available from all subspecialty areas, including T.P.N., Infectious Disease, Surgery, Urology and Physiotherapy. Full access to social workers, chaplaincy service, pharmacy, occupational therapy and dietetics is available and a weekly nursing conference is held with all support staff represented. More than 1,000 patients were admitted in 1990 at both the Women's Hospital and St. Boniface Hospital units.

Section Activities

The Section continues to be active locally, nationally and internationally. During the last year section members have had the privilege of serving in the following capacities:

1 Past President - Felix Rutledge Society
2. Executive Member - Gynecologic Oncologists of Canada
3. President - Gynecologic Oncologists of Canada
4. Council Member - Canadian Colposcopy Society
5. Member - Society of Obstetricians and Gynecologists of Canada, Oncology Committee
6. Treasurer - Society of Obstetricians and Gynecologists of Canada
7. Chairman - Written Exam Committee in Ob/Gyn - Royal College of Physicians and Surgeons of Canada
8. Vice Chairman - District VI American College of Obstetricians and Gynecologists.

Active participation on various NCIC committees continues, and current protocols, mainly in ovarian cancer, have been accrued. New protocols in endometrium, cervix and sarcomas are in the preparatory stages.

Within the Section current active research interests include:

a) Hemodilution in major gynecologic surgery
b) Surgical staging of endometrial carcinoma
c) Uterine and ovarian sarcoma chemotherapy
d) Flow cytometry in ovarian and endometrial carcinoma
e) The role of chemotherapy in ovarian tumors of low malignant potential.

SECTION OF GYNECOLOGIC ONCOLOGY STATISTICS
Manitoba Cancer Treatment and Research Foundation and
St. Boniface Oncology Clinic (1990)

	New Patients	Follow-up Visits	Total Patient Visits
	Clinic Visits		
1988	408	3391	**3799**
1989	437	4006	**4443**
1990	426	3760	**4186**
	Colposcopy Clinics		
1990	698	2799	**3497**

Hospital Admissions

	Health Sciences Centre	St. Boniface
Surgical	396	112
Non-surgical	407	227
Total	**803**	**339**

HEMATOLOGY LABORATORY

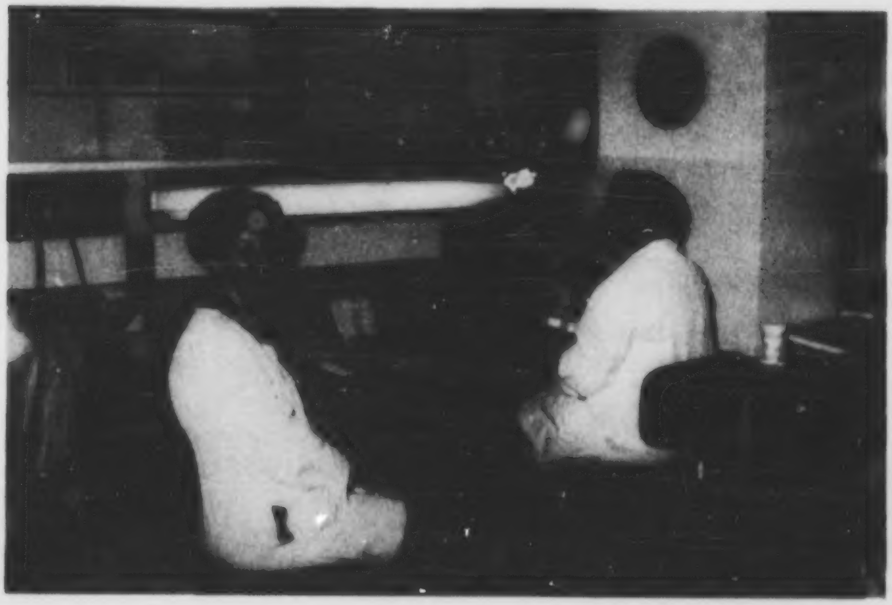
Brent Schacter, M.D., FRCPC, *Section Head*
Susan Tighe, R.T., *Head Technologist*

Technologists

Marlene Crielaard, R.T.
Jeannine Olivier, R.T.
Dianne Gamble
Leona St. Onge, R.T.

The Hematology Laboratory, located on the main floor of the Manitoba Cancer Foundation, is responsible for all routine hematological investigations, including bone marrow differentials, for the outpatient population of the Foundation. In February, the laboratory replaced its Coulter S Plus IV with a cap piercing Coulter JT II. A preliminary report can be available in a matter of minutes of obtaining a blood sample. The rapid reporting enables physicians to proceed with treatment without delay. Visual differentials and confirmation of values from the JT II are often necessary due to the abnormal nature of many of the blood profiles.

In 1990, 18,102 patient visits were recorded in the laboratory with a unit work value of 522,700.



HUMAN RESOURCES

Gloria Hanson, *Director*
Lucille Walesiak, *Administrative Assistant*

In mid-1990, a formal Human Resources Department was established, staffed by a Director and an Administrative Assistant.

The broad purpose of the Department is to provide the Foundation with an effective workforce, with specific objectives as follows:

1. To facilitate efficient and effective management of the Foundation;
2. To maximize the effectiveness of its human resource component;
3. To promote and maintain positive relationships with staff at all levels, and foster a cooperative working environment;
4. To support management development and growth of organizational skills in staff.

To achieve these objectives, services are provided in the following major areas:

- Recruitment/Selection/Employment
- Labour/Employee Relations
- Compensation Administration/Job Analysis
- Management Development/Staff Training
- Human Resource Management / Strategic Planning

In its first year of operation, efforts were primarily directed at addressing immediate needs, such as recruitment and labour relations, and operational development. Over 70 recruitments were undertaken, and a major collective agreement negotiated. Structures were set in place to formalize human resource systems, policies and procedures.

This growth and development will continue through the next years, with emphasis on ensuring future needs are addressed in context of the Foundation's overall strategic planning and facility expansion program.

INFORMATION SERVICES

Harvey Schipper, B.A.Sc., M.D., FRCPC, *Director*
Peter West, *Assistant Director*
Tim Siemens, Normand Chartier, *Programmer/Analysts*
Dianne Zimmer, *Data Entry Operator*

The primary responsibilities of the Information Services Department are to support the Records and Registry Department's information systems, provide computing support to other Manitoba Cancer Treatment and Research Foundation departments and implement a computerized Outreach Cancer Programme patient information management system. During the 1990/91 fiscal year, the Information Services Department has concentrated its attention and resources on Outreach Programme activities.

Records and Registry Department: Information Systems

Written in the COBOL programming language and implemented on a Prime 2550 Minicomputer, the Patient Information System and the Registry Information System comprise the Records and Registry information management resource. The Patient Information System controls master patient index transactions, which include patient registration and patient demographic inquiries/updates. The Registry Information System manages tumour information for all cases that have been reported to the MCTRF since 1937.

The Information Services Department manages the Records and Registry computer-based information resource, facilitating tumour data extractions and reporting (cases, incidence and mortality) compliant with all statutory requirements.

MCTRF Departments: Computing Support

The Epidemiology Department is another major user of the Information Services minicomputing resource. Statistical analysis software (SAS) and related research projects, programs and datasets reside on the minicomputer. Micro-computing support is provided on an informal basis.

The Foundation has also seen the number of personal computers increase and provides micro software support, etc., to the departments as required.

LIBRARY

Donna Chornenki, *Librarian*

The Library of the Manitoba Cancer Treatment and Research Foundation provides information in support of patient care, education, and research.

The library has implemented a fully integrated system of computerized literature searching using the Medlars System and Reference Update. 2213 literature searches were provided, an increase of 362 from last year.

A link to the University of Manitoba PALS system was established, giving the Foundation Library access to the collections of all the University of Manitoba libraries, St. Boniface Hospital, and Red River Community College.

The Foundation Library participated with 17 other Manitoba health libraries in publishing a new edition of the Manitoba Health Libraries Association list of Selected Serials. The Manitoba Health Libraries Association has a reciprocal arrangement for local lending and interlibrary loans.

At the end of the 1990 calendar year, the Manitoba Cancer Treatment and Research Foundation Library's holdings totaled 3422 books, 3308 bound journals, and 87 active subscriptions to journal material.

The library is in the process of redeveloping its patient information collection. Newer editions of literature on coping with cancer and treatment for patients and their families have been obtained with funds provided by the Canadian Cancer Society and books received in memory of Sandra Whitehead.

We acknowledge with gratitude the continuing support of the volunteer staff, who provided the library with 900 hours of dedicated service.

MEDICAL ONCOLOGY

MacCharles Unit

David M. Bowman, M.D., B.Sc.(Med.), FRCP(C), *Department Head*
S. Ireland, J. Powell, *Department Secretaries*

St. Boniface Unit

Harvey Schipper, B.A.Sc., M.D., FRCPC, *Department Head*
Mary McKee, *Department Secretary*

Medical Oncologists

E. Bow, M.D., M.Sc., D. Bact., FRCPC
L. Brandes, M.D.,B.Sc.(Med), FRCPC
J. Foerster, M.D. B.Sc.(Med)
G. Goldenberg, M.D., Ph.D., FRCPC
L.G. Israels, B.A., M.D., M.Sc., FRCPC
J. Johnston, M.D.,B.Ch.,FRCPC
M. Levitt, M.D., M.Sc., FRCPC
C. Olweny, M.B.Ch.B., M.(Med.), M.D., FRACP
B. Schacter, M.D., B.Sc.(Med.), FRCPC
H.Schipper, B.A.Sc., M.D., FRCPC
T. Shore, M.D., FRCPC
B. Weinerman, M.D., FRCPC

Clinical Fellows

J. Blondal
T. Corbett (Radiation Oncology)
A. Ilnyckyj (Radiation Oncology)
G. Michaud
C. Mihalcioiu

Residents

W. Czarnecki
A. Krahn
B. Roe
A. Wong

Clinical Investigations Office

Martin Levitt, M.D., M.Sc., FRCPC, *Director*
Stephan Larsson, M.B., Ch.B., FRCR, *Associate Director*
Erna Stiles, *Office Manager*
Kerry McDonald, R.N., *Senior Nurse*
Val Powell, R.N., *Research Nurse*
Leslie Costa, Kathy Hjalmarsson, Heidi Kampen, Darlene Penner, Debbie Timchishen, *Data Managers*

MacCharles Unit

The MCTRF Department of Medical Oncology's primary role is to provide exemplary care for patients with cancer in Manitoba through ambulatory clinics. Medical oncologists provide inpatient care during hospitalizations via the Health Sciences Centre and St. Boniface General Hospital.

All medical oncologists are also geographic full-time professional staff of the Department of Medicine, University of Manitoba, have major undergraduate and postgraduate teaching responsibilities, and conduct basic and clinical research related to cancer.

Further exemplifying their matrix roles, several medical oncologists serve in various capacities: Executive Director (MCTRF), Director of Palliative Care (Health Sciences Centre and Winnipeg Municipal Hospital), Director of Clinical Programmes (MCTRF), Section Head, Section of Hematology/Oncology, University of Manitoba, and Director of SBGH Oncology Unit and the Manitoba Cancer Outreach program.

During 1990, medical oncologists saw **669** new patients at the M.R. MacCharles out-patient unit (an increase of eleven percent over 1989), and provided care at **7,567** follow-up visits (an increase of seven percent). They also provided approximately **600** consultations at the Health Sciences Centre.

As new out-patient volumes at the M.R. MacCharles Unit have tripled in the past three years, the recent announcement of the MCTRF building expansion entailed major role planning for Medical Oncology, with all other departments. In addition to critical needs for clinic and research space, nursing and support staffing, we see major challenges including: 1) increased emphasis upon multidisciplinary care for cancer patients; 2) development of liaison programs with other urban institutions and programs in the community, including palliative care; 3) enhanced medical oncology recruitment; and 4) definition of the complex roles and responsibilities of medical oncologists inter-institutionally (MCTRF, University of Manitoba, HSC and SBGH).

The Department of Medical Oncology (M.R. MacCharles Unit) provides ambulatory care currently for adult cancer patients referred by physicians. Some 21 "half-day" (generally 4-6 hours each) clinics operate weekly. Multidisciplinary conjoint clinics with radiation and surgical oncology provide care for head and neck cancer, breast and lung cancer, soft tissue sarcomas and central nervous system neoplasms.

During 1990, we welcomed Dr. Charles Olweny, former Professor of Oncology from Adelaide, Australia, as a member of the SBGH Oncology Unit. We also observed the retirement of Dr. G. J. Goldenberg, after many years in the Department, upon his move to the University of Toronto. Dr. James Johnston was recipient of the Portney Research Award, and is on internal study leave (September 1990 to August 1991).

Visiting Professors to the Department during 1990 included: Dr. J. Yao (University of Texas), Dr. C. Baines (University of Toronto), Dr. R. Nash (Fred Hutchinson Cancer Centre), Dr. M. Rubinger (British Columbia Cancer Agency), Dr. J. Sternward (World Health Organization), Dr. M. Mitchell (University of Southern California) and Dr. F. Porzolt (University of Ulm, Germany).

During 1990, areas of special endeavour included the following:

1. The GD6 Oncology Unit is a 19 bed high efficiency air-filtered unit, located at the Health Sciences Centre. Its prime purpose is the provision of excellent care, with integrated research and teaching for patients with acute leukemia and high grade lymphomas, and incorporates a leukemia/bone marrow transplant service. Dr. Eric Bow relocated from SBGH July 1, 1990, as GD6 Service Chief, and during the year has established numerous clinical, research and teaching activities on the Unit.

2. The Bone Marrow Transplant Program of Manitoba was approved by MHSC in 1989,

as a joint program of MCTRF, HSC and the Canadian Red Cross Blood Transfusion Service. Under the Acting Directorship of Dr. B.Schacter during 1990, major detailed planning, recruitment and training activities were initiated in collaboration with Dr. T. Shore. The first Manitoba autologous bone marrow transplant was undertaken, with successful marrow engraftment, in November, 1990.

3. Medical oncologists continued to actively participate in the development of an MCTRF artificial intelligence computer-based "chemotherapy advisory system" which was enthusiastically piloted at the Brandon Outreach Unit during 1990.
4. After extensive re-evaluation visits by the Royal College of Physicians and Surgeons of Canada in February, 1990, both of our post-graduate programmes, in Hematology and Oncology, received full approval by the College.
5. After formal announcements late in 1989, a World Health Organization Collaborating Centre for Quality of Life Research in Cancer was established as part of the St. Boniface General Hospital Oncology Unit.

St. Boniface Unit

The intermediate and long term goal of the St. Boniface Unit of the Manitoba Cancer Foundation program is to develop a major focus of solid tumour expertise. This solid tumour expertise is to be developed and utilized in a multidisciplinary manner. Linked with the Cancer Foundation's Outreach Program, the goal is to develop a pattern of cancer management such that care can be delivered, as appropriate, in each tier of the health care system.

The starting point for our effort is medical care. We saw approximately four hundred and fifty new patients in 1990, managed with a medical staff complement of approximately two and a half equivalent full time physicians. Better than four thousand five hundred follow up visits were provided. While patients with acute leukemia, and those being prepared for marrow transplant are no longer seen at St. Boniface, we are gradually beginning to accept patients with colorectal tumours for which a standard of care requiring post surgical chemotherapy is coming to be accepted. In conjunction with the World Health Organization Collaborating Centre for Quality of Life Studies in Cancer Care, Dr. Charles Olweny has joined the St. Boniface staff, coming most recently from the Royal Adelaide Hospital, University of Adelaide in Australia, where he served as Head of Oncology. The year also brought very significant recognition to the Oncology nurses. In recognition of their excellence, Radiumhemmet, the Cancer Hospital at the Karolinska Institute in Sweden, proposed and initiated a formal exchange of site visits, and targeted areas for mutual exploration have been identified. The first formal exchange cycle is planned for the fall of 1991.

Oncology teaching has always been a high profile activity at St. Boniface Hospital. Medical residents rotating through the St. Boniface unit see a diversified mix of Oncology patients and are increasingly exposed to a multidisciplinary management environment. Much of the Cancer Foundation Outreach Program nursing training takes place at St. Boniface Hospital. A particularly interesting educational "experiment of one" was undertaken in 1990, in collaboration with the Department of Family Practice. A specially tailored Oncology training program for community physicians was developed for a single resident and is viewed as the precursor of expanded programs to follow. In a similar vein, the Undergraduate Medical curriculum in Oncology is in the process of substantive revision, with leadership and major participation from St. Boniface staff.

The development of a research infrastructure is a long term process. The focus for the short and intermediate term at St. Boniface Hospital is the development of clinical and outcome analysis expertise with a particular focus on health care delivery. With the opening of the W.H.O. Collaborating Centre in 1990, a major component of that research infrastructure has been established. The opening Symposium drew participants from government and academe, from Canada and from Europe. In addition to collaborative studies and clinical trials, members of the St. Boniface unit have conducted productive research focusing on acute leukemia, venous access systems, and a number of quality of life issues. The unit has been a strong focus of nursing research, and the Department of Social Work is in process of important work. In 1990, final plans were concluded for the approved expansion and total redevelopment of the Oncology outpatient facility. With construction underway, the new linear accelerator facilities, redeveloped outpatient clinic space, designed for multidisciplinary management, and a new administrative centre will be complete and operating by the summer of 1992. This is physical representation of a multidisciplinary management program that has become a significant priority for both St. Boniface Hospital and the Manitoba Cancer Foundation.

	NEW PATIENTS			FOLLOW-UP PATIENTS		
	MacCH	SBGH	TOTAL	MacCH	SBGH	TOTAL
1987	221	353	**574**	5268	4673	**9941**
1988	407	398	**805**	6371	4840	**11211**
1989	598	291	**889**	6901	4300	**11201**
1990*	669	472	**1141**	7567	5584	**13151**

* includes Dr. Shojania at SBGH

Basic Research

Drs. J. B. Johnston, G. J. Goldenberg, L. J. Brandes and B. A. Schacter as members of the Department of Medical Oncology are also senior members of the Scientific Staff of the Manitoba Institute of Cell Biology. Descriptive abstracts of their ongoing basic research are to be found in Cell Biology's separate report in this volume.

Clinical Investigation

New developments in medical therapy of cancer have made the conduct of a clinical investigation programme the cornerstone of developing cancer treatment programmes. In Medical Oncology, programmes of clinical investigation are carried out:

- on an independent basis whereby the Clinical Investigations Office assists investigators in developing proposals, formulating documentation, etc., however, the onus for this is on the individual investigator.
- in collaboration with major clinical trial cooperative groups.

The Protocol Review Committee, with multidisciplinary membership, evaluates and approves all new clinical protocols involving the Manitoba Cancer Treatment and Research Foundation patients. Committee membership includes Drs. M. Levitt (Chairman), D. Bowman, B. Weinerman, G. Krepart, and L.G. Israels.

The Department of Medical Oncology also participates in clinical trials sponsored by several national and international clinical trial co-operative groups, including the National Cancer Institute of Canada (NCIC - Principal Investigator - Dr. M. Levitt), and the National Surgical Programme for Breast and Bowel Cancers (NSABP - Principal Investigator, Dr. D. M. Bowman). Participation in numerous protocols with these co-operative groups and institutions remains a high priority of medical oncology. We believe these multi-institutional co-operative trials represent the forefront of developmental cancer therapeutics.

The Clinical Investigation Office, directed by Dr. M. Levitt, Medical Oncologist, coordinates all MCTRF clinical trials.

CLINICAL INVESTIGATIONS OFFICE PATIENT ACCRUAL - ADULT

STUDY GROUP:

NCIC	1989	1990
Remaining On-Study From Prior Years	307	307
New patient Accrual	28	28
Off Study	28	13
Remaining On-Study	307	322
NSABP		
Remaining On-Study From Prior Years	396	404
New Patient Accrual	29 + 84* = 113	48
Off Study	9 + 84* = 105	13
Remaining On-Study	404	439
RTOG (New Institution - Affiliate Member as of July 1988)		
Remaining On-Study From Prior Years	11	20
New Patient Accrual	10	10
Off Study	1	2
Remaining On-Study	20	28
LOCAL TRIALS		
Remaining On-Study From Prior Years	87	90
New Patient Accrual	31**	27
Off Study	28**	17
Remaining On-Study	90	100
TOTAL ON-STUDY (YEAR END)	821	889
PEDIATRICS		
Remaining On-Study From Prior Years	270	313
New Patient Accrual	56**	46**
Off Study	13	14
Remaining On-Study	313	345
TOTAL ON STUDY (YEAR END)	313	345

* Occupational Staff Health & Hazard Study (84 participants).

** Includes local and miscellaneous non-protocol patients.

The following is a brief description of active adult clinical investigative trials in 1990.

Disease Site	Number	Description
Lung Carcinoma	MBR 86.1	A randomized study to compare the toxicity and effectiveness of radiotherapy plus lonidamine with "standard" radiotherapy itself in patients with inoperable non-small cell lung cancers without distant metastases.
	MBR 89.1	SCHERING - A randomized Phase III extensive small cell carcinoma lung study; in patients who have Cyclophosphamide, Adriamycin and VP-16 administered x 6 cycles, followed by Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). Patients are randomized to various dose levels of GM-CSF: None, 10 or 20 mcg/kg.
	MBR 88.1	CARBO-CIS II - Study of Carboplatin and Cisplatin in combination with etoposide in previously untreated, small cell lung cancer and in combination with etoposide and bleomycin in previously untreated non-resectable non-small cell lung cancer.
Leukemia	MLK 88.5	Resistance to alkylating agents in chronic lymphocytic leukemia.
Bone Marrow	MBM 88.5	Phase I-II Trial of Thalidomide with or without cyclosporine in the treatment of refractory chronic graft-versus-host disease(GVHD).
	CBMTSG 89.01	A randomized clinical trial of intravenous CMV Immunoglobulin in patients undergoing Bone Marrow Transplant. CMV Immunoglobulin vs. No Treatment.
	CBMTS 89.04	Treatment of poor prognosis lymphoblastic lymphoma. To determine the efficacy of consolidation treatment with intensive chemo-radiotherapy and marrow transplantation for poor prognosis lymphoblastic lymphoma patients.
Multiple Myeloma	N.MY. 84.1	Pilot study of weekly Cyclophosphamide and alternate day Prednisone therapy (CWAP) as primary treatment in multiple myeloma Stage I-IV.
Malignant Melanoma	NCIC	Surgical study to determine the safest ME.5 excision margins around the primary melanoma and to evaluate the management of the regional lymph nodes. A national intergroup protocol.

Malignant Melanoma	NCIC ME.7	A clinical trial to compare immunomodulating doses of human interferon gamma with levamisole for the adjuvant treatment of poor prognosis malignant melanoma.
Colorectal Carcinoma	NSABP C-04	A clinical trial to assess the relative efficacy of 5-FU and Leucovorin and Levamisole in patients with Dukes' B and C carcinoma of the colon.
	NSABP R-02	A clinical trial to compare adjuvant MethylCCNU, Vincristine, 5-FU (MOF) with and without radiation in patients with Dukes' B and C carcinoma of the rectum. (Females are excluded from this study).
	NCIC CO.3	To determine whether adjuvant treatment with 5-FU and folinic acid versus control is effective in increasing survivorship and prolonging the disease free interval in patients undergoing curative resection of colonic adenocarcinomas. (Limited to Duke's B2 patients only).
	MCR	Hoffman-Laroche metastatic colorectal carcinoma (measurable disease). Roferon-A, 5-FU vs. 5-FU/Leucovorin. No prior chemotherapy or use of Interferon.
Breast Carcinoma	NCIC MA.4	To compare Tamoxifen VS Tamoxifen plus combination chemotherapy in patients with ER or PR positive stage II breast carcinoma.
	NSABP B-17	Randomized study to evaluate post-operative breast irradiation following segmental mastectomy plus axillary dissection in patients with non-invasive intraductal adenocarcinoma.
	NSABP B-19	A clinical trial to compare sequential Methotrexate 5-Fluorouracil with conventional Cyclophosphamide, Methotrexate and 5-FU in primary breast cancer patients with negative nodes and estrogen receptor negative tumors.
	NSABP B-20	A clinical trial to determine the worth of chemotherapy and Tamoxifen over Tamoxifen alone in the management of patients with invasive breast cancer, negative axillary nodes and estro gen receptor positive tumors.

Breast Cancer	NSABP B-21	A clinical trial to determine the worth of Tamoxifen and the worth of breast radiation in the management of patients with node-negative, occult, invasive breast cancer treated by lumpectomy.
	NCIC IND.45	Phase II clinical trial of patients with evaluable metastatic breast cancer utilizing oral menogaril; to determine efficacy and toxicity.
	MB 88.3	Epirubicin high dose VS conventional dose in metastatic breast cancer. A randomized study in women after CMF failure.
Prostate Carcinoma	PR 84.1	Phase III randomized Megestrol Acetate plus low dose stilbestrol VS Diethylstilbestrol in Stage D^2 prostate cancer.
	PR 88.4	A comparison of Flutamide capsules VS Flutamide tablets in previously untreated prostate cancer patients.
	RTOG 85-31	Phase III study of Zoladex adjuvant to radiotherapy in unfavorable prognosis carcinoma of the prostate.
	RTOG 86-10	Phase III study of Zoladex and Flutamide used as cytoreductive agents in locally advanced carcinoma of the prostate treated with definitive radiotherapy.
Pancreas Carcinoma	MPA.89.1	A clinical trial to assess survival and toxicity in patients with Stage 2,3, or 4 of pancreatic carcinoma utilizing 5-FU and leucovorin.
Renal Carcinoma	NCIC IND.46	A phase II clinical trial in patients with metastatic renal cell carcinoma who have had no prior chemotherapy utilizing the drug LY186641 to determine efficacy and tumor response.
Symptom Control	NCIC SC.6	A clinical trial to assess the antiemetic efficacy, tolerance, and safety of GR38032F versus Dexamethasone plus metoclopramide in patients with breast cancer receiving: CMF (cyclophosphamide, methotrexate, and 5-FU).

Symptom Control	NCIC SC.7	A double-blind clinical trial to assess the efficacy and safety of six doses of the antiemetic BMY-25801 and Methylprednisolone among patients receiving moderately emetogenic chemotherapy.
Brain Tumor	NCIC IND.54	Phase II study of Tiazofurin in malignant glioma recurrent primary brain tumors.

Publications

Begleiter, A., Jesson, M.I., and Johnston, J.B. Uptake and binding of 3'-(3-cyano-4-morpholinyl)-3'-deaminoadriamycin and 3'-(4-morpholinyl)-3'-deaminoadriamycin in L5178Y lymphoblasts in vitro. Cancer Communications. 2:7-12, 1990.

Brandes, L.J., and Hogg, G.R. Study of the in vivo antiestrogenic action of N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine.HCl (DPPE), a novel intracellular histamine antagonist and selective antiestrogen binding site ligand. J. Reprod. Fert., 89:59-67, 1990.

Fisher, B., Redmond, C., Legault-Poisson, S., Dimitrov, N.V., Brown, A.N., Wickerham, D.L., Wolmark, N., Margolese, R.G., Bowman, D., Glass, A.G., Kardinal, C.G., Robidoux, A., Jochimsen, P., Cronin, W., Deutsch, M., Fisher, E.R., Myers, D.B., and Hoehn, J.L. Postoperative chemotherapy and Tamoxifen compared with Tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to Tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. J. of Clin. Oncol., 8:1005-1018, 1990.

Fisher B, Costantino J, Redmond C, Poisson R, Bowman D. et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. NEJM. 1989;320(8):479-484, 1989

Fisher B, Redmond C, Dimitrov NV, Bowman D, et al. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor negative tumors. NEJM. 1989;320(8):473-478.

Johnston, J.B., Israels, L.G., Goldenberg, G.J., Anhalt, C.D., Pugh, L., Mowat, M.R.A. and Begleiter, A. Glutathione transferase, sulfhydryl groups and DNA crosslinking activity with chlorambucil in chronic lymphocytic leukemia. J. Natl. Cancer Instit. 82:776-779, 1990.

Johnston, J.B., Israels, L.G., Goldenberg, G.J., Anhalt, C.D., Pugh, L., Mowat, M.R.A. and Begleiter, A. Glutathione transferase, sulfhydryl groups and DNA crosslinking activity with chlorambucil in chronic lymphocytic leukemia. J. Natl. Cancer Instit. 82:776-778, 1990.

Olweny, C., Castwolds modification of the Ann Arbor staging system for Hodgkin's disease [Letter]. J. Clin. Oncol., 18:1958, 1990.

Orr, K.B., Foerster, J. An ELISA procedure to detect anti-double stranded and anti-single stranded DNA binding antibodies. J. Lab. Clin. Analysis, 4:328, 1990.

Schipper, H. "Quality of Life: Principles of the Clinical Paradigm." J. of Psychosocial Oncol., 8:2-3, 1990.

Shore, T., Barnett, M., Phillips, G. An unusual case of fatal methotrexate toxicity. Med. and Ped. Oncol., 18:159-161, 1990.

Shore, T., and participants of a Terry Fox Cancer Research Workshop. Status of autologous bone marrow transplantation in Canada. Annals of Royal College of Physicians and Surgeons of Canada, 23:1, 57-58, 1990.

Shore, T., Nelson, N., and Weinerman, B. A meta-analysis of stages I and II Hodgkin's disease. Cancer, 65:1155-1160, 1990.

Schacter, B. and Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life. Brit. Med. J., 300:573-578, 1990.

Weinerman, B., Maruoun, J., Stewart, D., Cripps, C. and Johnston, J.B.. Sequential methotrexate, 5-fluorouracil and leucovorin in metastatic measurable colorectal cancer. Does it work? Cancer Investigation, 8:339-343, 1990.

Abstracts

Begleiter, A., Jesson, M.I. and Johnston, J.B. Uptake and binding of the morpholino analogues of Adriamycin, CMA and MA, in L5178Y lymphoblasts in vitro. Proc. Am. Assoc. Cancer Res., 31:349, 1990.

Fisher, B., Redmond, C., Poisson, S., Dimitrov, N., Margolese, R., Bowman, D., Glass, A., Robidoux, A., Wickerham, D., Wolmark, N., Jochimsen, P. Increased benefit from addition of Adriamycin and cyclophosphamide (AC to Tamoxifen (TAM, T) for positive-node TAM-responsive postmenopausal breast cancer patients: Results from NSABP B-16. Proc. Am. Soc. of Clin. Oncol., 9:20, 1990.

Fisher, B., Brown, A.N., Dimitrov, N.V., Poisson, S., Redmond, C., Margolese, R.G., Bowman, D., Wolmark, N., Wickerham, D.L., Kardinal, C.G., Shibata, H., Patertherapy compared with 6 months of cyclophosphamide, methotrexate and fluorouracil in positive-node breast cancer patients with Tamoxifen-nonresponsive tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15. J. of Clin. Oncol., 8:1483-1496, 1990.

Israels, L.G., Jesson, M.I., Israels, S.J., Greenberg, A.H., Begleiter, A., Mowat, M.R.A. and Johnston, J.B. Activity of TGF- in chronic lymphocytic leukemia (CLL) in vitro. Blood, 76(Suppl):283, 1990.

Reece, D., Barnett, M., Bow, E., Klingemann, H.G., Shepherd, J., Shore, T., Phillips, G. High-dose Cytosine Arabinoside (HD ARA-C) Etoposide (VP-16) and Daunorubicin (DNR) for induction and consolidation therapy of adult acute myelogenous leukemia (AML). Clin. and Invest. Med., The Royal College of Physicians and Surgeons of Canada Meetings, page B48, Toronto, Ontario, September 14-17, 1990.

Schipper, H. "Measurement of Quality of Life in Cancer Patients." Proc. of 2nd Ann. Meeting of the Japan Psycho-Oncology Soc., Tokyo, Japan. Cancer Patients and Palliative Care, 1990 - Japanese.

Shore, T. Bone marrow, state of the art. Manitoba Medicine, Spring, 1990.

Smithgall, T.E., Johnston, J.B., and Glazer, R.I. Detection of C-fes proto-oncogene mRNA in human myeloid leukemia by RNase protection assay. Proc. Am. Assoc. Cancer Res., 31:314, 1990.

Stelmack, G.L., Leith, M., Begleiter, A., and Goldenberg, G.J. Increase of gene copy number and expression of glutathione S-transferase (GSTs) in quinone-resistant L5178Y murine leukemia. Clin. Invest. Med., 13:B121, 1990.

Verburg, L., Begleiter, A., Israels, L.G. and Johnston, J.B. Mechanisms involved in inhibition of repair of irradiation-induced DNA strand breaks (SB) in L5178Y lymphoblasts by 2'-deoxycoformycin (dCF) and deoxyadenosine (dAdo). Proc. Am. Assoc. Cancer Res., 31:389, 1990.

Wickerham, D., Fisher, B., Brown, A., Dimitrof, N., Poisson, R., Redmond, C., Margolese, R., Bowman, D., Wolmark, N., Kardinal, C., Shibata, H., Patterson, A., and Wolter, J. Two months of Adriamycin-Cyclophosphamide (AC) with and without interval reinduction therapy vs. six months of conventional CMF in positive-node breast cancer patients non-responsive to Tamoxifen: Results of NSABP B-15. Proc. of the Am. Soc. of Clin. Oncol., 9:20, 1990.

MEDICAL PHYSICS

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Secretaries

Thelma Davidson
Carla Webb
Linda Peebles

Awards and Honours

ALLAN M. SOURKES, PH.D.

appointed to the RADIATION REGULATIONS COMMITTEE of the *Canadian Organization of Medical Physicists.*

SHLOMO SHALEV, PH.D.

was an INVITED SPEAKER at the *AAPM Spring Seminar*, San Diego.

was an INVITED SPEAKER at the *Beijing International Congress on Radiation Physics.*

was a SYMPOSIUM SPEAKER at the *Memorial Sloan-Kettering Cancer Center*, New York.

was an INVITED SPEAKER at the *Akademisch Ziekenhuis - Vrije Universiteit*, Brussels.

was an INVITED SPEAKER at the *Royal Marsden Hospital and Institute of Cancer Research*, Sutton, England.

Post -Doctoral and Student Awards

KONRAD LESZCZYNSKI, M.SC.

received a STEVE FONYO STUDENTSHIP from the *National Cancer Institute of Canada.*

GEORGI GLUHCHEV, PH.D.

received a VISITING SCIENTIST award to work at *Manitoba Cancer Treatment and Research Foundation* from February 1991 to January 1992.

KIARAN MCGEE, M.SC.

received a *Manitoba Cancer Treatment and Research Foundation* STUDENTSHIP.

Seminar Speakers

Acupuncture - An Overview
Dr. S. Larsson, Department of Radiology, Manitoba Cancer Treatment and Research Foundation

Chaos and Fractals
B.W. Southern, Ph.D., Department of Medical Physics, University of Manitoba

Iodine 125 Brain Implants and Progress on the Electron Loss Model
G. Sandison, Ph.D. , Department of Radiation Oncology, Indiana University School of Medicine

Three-Dimensional Visualization of Medical Images from Multiple Modalities
Three-Dimensional Cerebral Angiography with MRI
T. Peters, Ph.D., Dept. of Neuroradiology and McConnell Brain Imaging Unit, Montreal Neurological Institute, McGill University, Montreal, Quebec

Pion Therapy at Triumf
N. Davison, Ph.D., Department of Physics, University of Manitoba

Health care in the 1990's: The Management Challenge
Dr. J. Horne, Senior Vice-President, Corporate Planning and Development, Health Sciences Centre

Evaluation of Cerebral Blood Flow with HMPAO and ECD: A Radiopharmaceutical Perspective
Dr. D. Abrams, Radiopharmacy, Health Sciences Centre, Winnipeg
Dr. A. Peterdy, Nuclear Medicine Department, Health Sciences Centre and St. Boniface Hospital, Winnipeg

Physics Research at the Institute of Cancer Research/Royal Marsden Hospital UK
W. Swindell, Ph.D., Head, Radiotherapy and X-Ray Physics ICR/RMH

Stereo Lithographic Model Building
R. Palser, Ph.D., Department of Medical Physics, Manitoba Cancer Treatment and Research Foundation

Biomagnetic Imaging (BMI)
W. Huda, Ph.D., Department of Medical Physics, Manitoba Cancer Treatment and Research Foundation

In Vivo Measurement of Microvascular Permeability in Brain Tumours
T. Lee, Ph.D., St. Josephs Hospital and John P. Robarts Research Institute, London, Ontario

Medical Physics in Sheffield: Something old, something new...
J. Hermans, Ph.D. , Medical Physics Department, Northern General Hospital, Sheffield, England

Treatment Time Calculation
J. Thekkumthala, Ph.D., Thunder Bay, Ontario

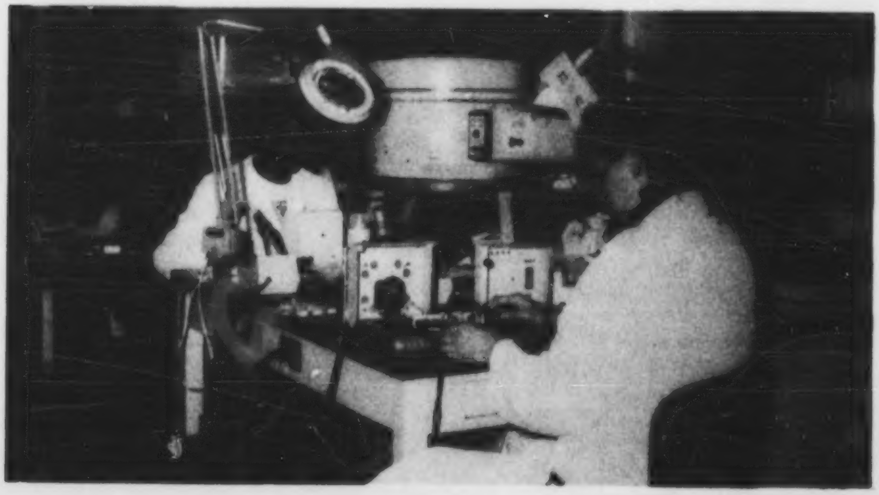
This year has seen the successful installation and commissioning of the Siemens MX-2 linear accelerator. This 6MV machine has replaced an older obsolete 4MV accelerator and is operating reliably with a clinical load of approximately 25 patients per day. Planning for the new linear accelerator at St. Boniface is continuing, and we look forward to the installation of this machine in early 1992. The 15-year-old Sagittaire accelerator and the 28-year-old Cobalt "F" treatment unit have continued to give valuable service, however, they will have to be replaced in the next few years.

The on-line portal verification system developed in the Department was used for clinical evaluation studies, and the treatment planning computer was upgraded, using research funds, to permit the use of CT-based planning techniques.

During the year a total of 2,804 simulations were performed, and 642 plans were prepared ranging from calculations for standard shielding to complicated dose distributions using CT data. The simulator filing system (with over 4,000 files) was changed from alphabetical to numerical order to correspond to the Cancer Registry number.

The Nuclear Electronics Section continued to provide technical support, service and preventative maintenance of equipment in all Nuclear Medicine Departments in Winnipeg hospitals as well as the Radiotherapy Departments at MCTRF and St. Boniface General Hospital. Service is also provided to the Institute of Cell Biology when not in conflict with clinical priorities. The Section continued to participate in the design and fabrication of custom medical products, for use both within the MCTRF and in the general medical community, and Section personnel provided consultation in electronic matters to Nuclear Medicine, Radiotherapy and Medical Physics.

A major upgrade was carried out on the dual energy KD-2 linear accelerator, and a succession of problems with this unit lead to extensive downtime. During the year a new Co^{60} source was installed in the AECL Theratron 780 at St. Boniface General Hospital. The Nuclear Medicine Departments at various hospitals experienced no major equipment breakdowns. A new Siemens Lem gamma camera and computer system was installed at Grace Hospital. One of our technologists attended a five week factory training course in California on the Siemens KD-2 linear accelerator, and two technologists attended a two week factory training course in Haifa, Israel on an Elscint SPECT gamma camera and computing system.



The Section of Medical Devices saw many changes in 1990 with the retirement of the Section Head, Senior Designer, and machinist. This resulted in the re-appointment of existing staff and the hiring of new staff. The Section's continued ability to provide technical services, which demand a diverse range of skills, was ensured by the organization of in-house instructional courses in specialty welding, pantomilling and AutoCad. In addition to providing regular maintenance of Radiotherapy equipment at the Foundation and St. Boniface, the Section continued to provide service to Nuclear Medicine and other departments within the Foundation and Health Sciences Center. Some of the more major repairs undertaken during the year involved the KD-2 linear accelerator and related equipment. Extensive modifications were carried out to the Portal Imaging unit, treatment room door emergency release mechanism and defining head. A new control arm for the St. Boniface clinic is now in the final stage of completion. Modifications were made to several treatment couches for the Bone Marrow Transplantation program and a number of patient treatment aides were fabricated.

In 1990, the Mould Room recorded a total of 895 visits. In addition to fabricating positioning aids and related shielding, the staff instructed six R.T.T. students in the basic skills and techniques required to construct these devices. A pressure face mask was constructed for the HSC Burn Unit.

During 1990, the Medical Imaging Section continued its support of radiology and nuclear medicine activities in the teaching hospitals and elsewhere in the province. Several major pieces of equipment were commissioned and their quality control programs established. These include the magnetic resonance scanner at St. Boniface General Hospital together with several diagnostic x-ray units, a mobile x-ray unit at the Childrens Hospital, and a gamma camera and computer system at Grace General Hospital. Evaluations of new and potentially useful equipment were made for various hospitals, the nuclear medicine and computed tomography quality control programs were maintained, and clinical support was provided in the use of several pieces of equipment.

The Radiation Protection Section continued to carry out its mandated province-wide radiation protection activities, which include administration of Manitoba's X-ray Safety Regulation and carrying out surveys of non-ionizing radiation emitting devices. Radiation protection services were also provided for the Manitoba Cancer Foundation's activities in radiation therapy, including leakage compliance measurements on the newly commissioned 6MV linear accelerator facility, and a successful application for a "licence to construct" a new dual energy photon facility to be located at the St. Boniface Radiotherapy Unit. Activities carried on outside of the Foundation included radiation safety surveys in medical, dental, chiropractic, educational and commercial facilities.

Teaching has remained a high priority, and educational programs are in place for technologists, Residents in radiotherapy, radiology, and nuclear medicine, post-doctoral Fellows, and graduate students earning M.Sc. and Ph.D. degrees in Medical Physics.

Research Reports

CLINICAL IMPLEMENTATION OF ON-LINE PORTAL IMAGING

S. Shalev, S. Ryder, S. Cosby, K. McGee, S. El-Sayed, S. Larsson

We have implemented an on-line portal imaging system for routine clinical evaluation of portal beam alignment. Using a metal/phosphor detector and a sensitive video camera, the system acquires portal images at video rate (30 frames/sec), which are summed into "shots" of typically 0.5-1 seconds duration. The detector enclosure collapses in order to provide free access to the patient during set-up. Correction for screen and camera non-uniformity is performed automatically, and the contrast-enhanced images are displayed on-line during the treatment. Both static and dynamic portal images are available for post-treatment review, and time-lapse sequences of images from sequential treatments can be displayed in the form of a movie loop. Studies are underway of the magnitude of localization errors, and the utility of automated verification of field size and shape.

THE OPIUM PROJECT

S. Shalev, S. Cosby, K. Miskiewicz

Development continues on the computer software package known as OPIUM (On-line Portal Imaging University of Manitoba) in collaboration with Siemens Medical Laboratories. The system provides immediate verification of treatment fields, and is undergoing beta testing under clinical conditions in the Department. Improvements in the software include a more user friendly interface, storage of images on removable 600 MB optical disks, and increased reliability with automatic image acquisition and display. A comprehensive testing procedure was developed to evaluate all possible system functions and identify "bugs" or inconsistencies in the code. New algorithms under development include corrections for non-uniformities, real-time image processing, and post-processing for interactive image enhancement.

THE QUANTIFICATION OF RADIATION TREATMENT ACCURACY

S. Shalev, X. Ding, R. Strachan, S. Ryder, K. McGee

Conventional verification of beam size, shape, and position is based on portal films exposed weekly during the treatment, with visual comparison against a simulator x-ray film. Recently, on-line portal imaging has provided the capability of digital imaging during every treatment fraction, with the promise of on-line verification of treatment accuracy. However, automatic image processing and analysis is required to exploit the full potential of this approach. The comparison of a simulator image and a portal image is a three-step process. First, the two images are aligned by identifying corresponding fiducial points. We have compared the conventional method using regression analysis with a modification of the Procrustes technique based on a rho-theta plot, and have shown that this approach has a number of important practical advantages. Second, the portal beam size, shape and position are compared with the prescribed values. We evaluated a number of parameters useful for this purpose, including beam areas, beam edge displacements, centroid shifts, and transformation parameters (translation, rotation, scale). Third, the changes in beam size, shape, and position over a sequence of treatment fractions must be displayed in a meaningful way to the operator. We have investigated a number of alternative approaches to this, including a colour-wash image which shows the degree of over- or under-irradiation summed over all previous treatment fractions.

DIGITAL ENHANCEMENT OF ON-LINE PORTAL IMAGES: AN OBSERVER STUDY

S. Shalev, K. Leszczynski

On-line portal images exhibit poor spatial and contrast resolution, and are usually processed before display. Selective Contrast Limited Adaptive Histogram Equalization (SCLAHE) has been proposed as the digital enhancement procedure of choice, and we have carried out an observer study to evaluate the efficacy of this approach. The test data set consisted of eleven randomly selected images of the head and neck, acquired with an on-line portal imaging system. Each image was processed by SCLAHE, and presented to three observers in the original and processed forms, together with the digitized simulator film image on which anatomical landmarks had been identified. The observers were required to locate the corresponding landmarks on the portal images, and note was taken of the time required and the accuracy with which the points were located. Only 91% of the landmarks could be identified in the original images, but 100% were found in the processed images, showing that digital processing is preferable ($p<0.005$). Consistency in landmark localization was evaluated with the Wilcoxon signed-rank test, and the enhanced images were found to be superior in this regard ($p<0.001$). The results show that digital enhancement reduces the number of undetectable landmarks, and improves the accuracy with which they can be located. There was no significant reduction in the time required. The observer study has been shown to be a useful method of evaluating portal image quality.

THREE DIMENSIONAL PLANNING FOR RADIATION THERAPY

D.A. Viggars, S. Shalev, S. El-Sayed, S. Larsson, M. Stewart, B. Hintz

This retrospective study is intended to investigate the clinical feasibility of three dimensional treatment planning and determine the significance of the changes in patient treatment which would result from the use of three dimensional planning. Patients who have been treated by conventional two dimensional techniques, using CT scans to determine the target volume, are re-planned in this study by the following techniques: a) the beam parameters used in the treatment are used to calculate a full three dimensional dose distribution, b) beam weights and angles are kept the same as in a), but the beams are shaped conformally to match the target volume, c) a new set of beams is designed with complete freedom in choice of angles, weights and beam shape. After three dimensional dose calculations have been completed for all these techniques, the distributions are evaluated using dose-volume histograms and the OSCAR technique is used to determine the clinical significance of any differences between the distributions. This project is at a preliminary stage, but it is already clear that the major obstacle to the clinical implementation of three dimensional treatment planning is the length of time required by the radiation oncologist to define the target volume and outline the dose limiting structures on multiple CT-slices. Improved computer aids for this process will be necessary in the clinic.

OPTIMIZATION OF GIVEN DOSE USING DOSE-VOLUME CONSTRAINTS

D.A. Viggars, S. Shalev, J. Gatschuff, M. Stewart

Conventionally the radiation dose to be delivered to a patient is prescribed by the oncologist at some fixed point in the patient. This has the following disadvantages: a) it fails to provide guidance to the planning technologist on what dose levels are tolerable in dose limiting structures, b) it does not specify the uniformity of dose required in the target volume, c) a single point may be unrepresentative of the dose distribution as a whole. In earlier work we introduced the concept of the "OSCAR" dose-volume prescription, which was intended to allow the evaluation of a proposed treatment plan in terms of quantitative figures of merit or "scores" for the target and dose limiting structures. This has now been extended to determine an optimum dose level for each plan, by calculating all the scores for a particular plan as a function of the dose given to some specified point.

The oncologist can then choose the value of this dose which provides, in his view, the best compromise between the requirements of all the constraints he specified in the OSCAR prescription. This procedure has been programmed into the Theraplan treatment planning system and will be made commercially available by Theratronics International Ltd.

TREATMENT PLANNING FOR NON-RIGID PATIENTS

D.A. Viggars, S. Shalev, M. Stewart, W. Yu

Conventional treatment planning assumes that patients are immobile rigid bodies which can be positioned with exact reproducibility on the simulator and CT-scanner, and during each fraction on the treatment machine. These assumptions are clearly false, and earlier studies have shown that their violation may lead to clinically significant deviations of the actual dose distribution from the planned distribution. We are developing techniques for calculating dose distributions which take into account realistic uncertainties in the position of the patient during treatment. This is being done by two methods. In the first we calculate the dose distribution for the patient in the "intended" position and also in eight nearby positions which span the range of uncertainty in the actual position of the patient during treatment. We then construct a "realistic" dose distribution which is an average over the nine distributions already calculated, weighted to take account of the probability of finding the patient in each of the nine positions and the differences in dose due to the different relative positions of the machine and patient in the different patient positions. The second method attempts to reduce the computational burden created by the first method. It does this by applying a convolution procedure to the dose distribution calculated for the intended position. The essential problem in this method is to find a kernel for the convolution procedure which will correctly simulate the averaging procedure used in the first method. Initial investigations using single beam distributions indicate that it will be possible to find a kernel which will provide reliable results in the clinically interesting regions of the dose distribution.

TREATMENT PLANNING SOFTWARE DEVELOPMENT

D.A. Viggars, D.K. McCracken, J. Gatschuff

Software development this year has concentrated on improving the ease and speed with which information on targets and sensitive organs can be entered into the treatment planning computer by oncologists and technologists. The two main areas of interest have been a) the automatic addition of margins of specified width to a tumour, b) contour entry using a digitizer pen. Margins are required by many treatment protocols and it has previously been a difficult and time consuming task to create them with even moderate precision. We have provided a function in the Theraplan system which, in a few seconds, automatically adds a margin of user-specified width to any contour on a CT slice. The present system of contour entry on Theraplan requires the user to coordinate the use of a trackball, the keyboard and the display screen, and is found inconvenient by many users. In response to these difficulties we have developed a means of using the digitizer pen to "draw" contours on the screen in a natural way, with a simple "go-back and re-draw" facility. Use of the keyboard is not required while a contour is being drawn. Both these programs, and a number of other minor improvements in contour entry have been incorporated into the Theraplan system.

REGIONAL CEREBRAL BLOOD FLOW

R. Palser, M. Mirzai

A computer simulation of the measurement of regional blood flow is under development. A four compartmental model and the radiopharmaceutical Tc-99mm-HMPAO are being used together with arterial blood activity concentration curves to determine the blood flow to regions of the brain.

STEREO LITHOGRAPHIC MODEL BUILDING

R. Palser

Stereo lithography is a recently introduced engineering technique for the construction of three dimensional solid models. Two dimensional computed tomographic images are being used to construct models of bone and soft tissue for possible application in areas of reconstructive surgery, musculoskeletal trauma to the spine, and vessel and tumour visualization. The advantage of this technique over conventional methods that employ a numerically controlled multi-axis milling machine is that models containing internal cavities and much detail can be readily constructed.

MEASUREMENT OF X-RAY TUBE FOCAL SPOT SIZE

K. Chantziantoniou, A.M. Sourkes

A Digital Imaging Computer-System Method was successfully developed that can evaluate the dimensions of a diagnostic x-ray tube focal spot over a wide range of sizes and demonstrated over diagnostic range 0.1 - 1.2 mm nominal size. The method involved digitizing the x-ray image of a specially designed parallel wire focal spot test tool and evaluating the results using an appropriately designed algorithm applied to the digitized image of the test tool image captured by a television camera using frame-grabbing and digitizing computer electronics.

Publications

Baker, M., Huda, W., Stern, S. Count-based ratios for determining ventricular volumes. (Letter). *Journal of Nuclear Medicine,* **32:** 1312-1313, 1991.

Bews, J., Dunscombe, P., Lee, T., McClarty, B., Kroeker, M. The Role of Quantum Noise in the Measurement of Cerebral Blood Flow and Partition Coefficient Using Xenon Enhanced Computed Tomography. *Phys. Med. Biol.,* **35:** 937-945, 1990.

Bews, J., Dunscombe, P., St. Lawrence, K., McClarty, B., Kroeker, M. A Simplified Method for Measuring Cerebral Blood Flow with Xenon Enhanced Computed Tomography. *Clin. Phys. Physiol. Meas.,* **12 (3),** 1991.

Dunscombe, P.B., Fox, K., Ryder, S. A proposal for the classification of field placement errors in radiotherapy. *Medical Dosimetry,* **16:** 1-5, 1991.

Froese, G., Das, R.M., Dunscombe, P.B. The sensitivity of the thoracolumbar spinal cord of the mouse to hyperthermia. *Radiation Research,* **125:** 173-180, 1991.

Froese, G., Dunscombe, P.B., Das, R.M., McLellan, J. Thermal dosimetry of spinal cord heating in the mouse. *International Journal of Hyperthermia,* **6:** 319-332, 1990.

Hahn, P., Shalev, S., Viggars, D., Therrien, P. Treatment planning for protocol-based radiation therapy. *Int. J. Rad. Onc. Biol. Phys.,* **18:** 937-939, 1990.

Huda, W., Sourkes, A.M., Bews, J.A., Kowaluk, R. Radiation Doses Due to Breast Imaging in Manitoba: 1978 - 1988. *Radiology,* **177:** 813-816, 1990.

Huda, W., Bews, J. Population Irradiation Factors (PIF's) in Diagnostic Medical Dosimetry. *Health Physics,* **59:** 345-347, 1990.

Huda, W., Bews, J., Gordon, K., Sutherland, J., Sont, W., Ashmore, J. Occupational Doses to Medical Radiation Technologists in Manitoba (1978-1988). *Canadian Journal of Radiation Technologists*, **22:** 23-25, 1991

Huda, W., Kozak, R. Thyroid cancer hits Chernobyl "kids". *Australian Dr. Weekly*, 8 March 1991: 30-31.

Huda, W., Sandison, G.A. Effective dose equivalent, H_E, and positron emission tomography. *European Journal of Nuclear Medicine*, **17:** 116-120, 1990.

Huda, W., Bissessur, K. Effective dose equivalents, HE, in diagnostic radiology. *Medical Physics*, **17:** 998-1003, 1990.

Huda, W., Gordon, K., Greenberg, I.D. Diagnostic thyroid procedures and corresponding radiation doses in Manitoba: 1981-1985. Health Physics, **59**: 287-293, 1990.

Lees, T., Ellis, R., Dunscombe, P., McClarty, B., Hodson, D., Kroeker, M., Bews, J. Quantitative Computed Tomography of the Brain with Xenon Enhancement: A Phantom Study with the GE9800 Scanner. *Phys. Med. Biol.*, **35**: 429-439, 1990

Leszczynski, K., Shalev, S., Cosby, S. An adaptive technique for digital noise suppression in on-line portal imaging. *Physics in Medicine and Biology* **35** 429- 439, 1990

Leszczynski, K., Shalev, S., Cosby, S. A digital video system for on-line portal verification *SPIE*, **1231:** 401 - 405, 1990

McLellan, J., Sandison, G.A., Papiez, L., Huda, W. A restricted angular scattering model for electron penetration in dense media. *Medical Physics*, **18:** 1-6, 1991.

Palser, R.F., Jamieson, R., Sutherland, J.B., Skibo L. Three Dimensional Lithographic Model Building from Volume Data Sets. *Can. Assoc. Radiol. Journal*. **41:** 339-341, 1990.

Shalev, S., Viggars, D., Carey, M., Hahn, P. The objective evaluation of alternative treatment plans: II Score functions. *Int. J. Rad. Onc. Biol. Phys.* **20,** 1067-1073, 1990.

Shalev, S., Leszczynski, K., Cosby, S., Chu, T. Recent advances in portal imaging: The application of digital image processing techniques. *Electronic Imaging West 90, Passadena*, 550-552, 1990.

Soubra, M., Dunscombe, P.B., Hodson, D.I., Wong, G. Some physical aspects of external beam radiotherapy for the treatment of malignant pleural mesothelioma. *Int. J. Radiol. Oncol. Biol. Physics*, **18:** 1521-1527, 1990.

Viggars, D.A., Shalev, S. Colour graphics for 3D treatment planning. *Proc. Conf. "The Use of Computers in Radiation Therapy", Lucknow, India, Nov. 1990.* Eds: Hukku, S., Iyer, P.S., 111 - 114.

Viggars, D.A., Shalev, S. Dose optimization in 3D treatment planning. *Proc. Conf. "The Use of Computers in Radiation Therapy", Lucknow, India, Nov. 1990.* Eds: Hukku S., Iyer, P.S., 308 - 311.

Published Abstracts

Huda, W., Sourkes, A.M. Occupational Doses to Medical Radiation Technologists in Canada (1978 - 1988). *Radiology Supplement,* **177:** 173, 1990.

Leszczynski, K., Shalev, S., Cosby, S. A digital video system for on-line portal verification. *SPIE Medical Imaging IV Conference, Newport Beach, February 1990.*

Leszczynski, K., Shalev, S., Cosby, N.S. The imaging performance of a prototype digital video system for radiotherapy verification. *Medical Physics '90 Congress, Oxford, September 1990.*

Leszczynski, K., Shalev, S., Ryder, S. A study on the efficacy of digital enhancement of online portal images. *WESCAN Annual Meeting, March 1991.*

McGee, K., Shalev, S. 2D FFT filtering for online portal images. *WESCAN Annual Meeting, March 1991.*

Mirzai, M., Palser, R.F. Determination of flow and rate constants in a compartmental model of TC-99m-HMPAO in human brain. *The Journal of Nuclear Medicine,* **31:** 868, 1990.

Palser, R.F., Jamieson, R., Sutherland, J.B., Skibo, L. Stereo Lithographic Model Building. *Prairie Provinces Chapter Meeting, Society of Nuclear Medicine, Regina, Canada, April 1990.*

Palser, R.F., Jamieson, R., Sutherland, J.B., Skibo, L. Stereo Lithographic Model Building. *Canadian Organization of Medical Physicists Meeting, Montreal, Canada, June 1990.*

Palser, R.F., Jamieson, R., Sutherland, J.B., Skibo, L. Stereo Lithographic Models. *Canadian Medical and Biological Engineering Society Meeting, Winnipeg, Canada, June 1990.*

Shalev, S., Chu, T., Cosby, S. Computerized portal film analysis of beam localization errors. *Medical Physics,* **17:** 554, 1990.

Shalev, S., Leszczynski, K., Cosby, S., Agbay, H. Clinical implementation of on-line portal imaging. *Medical Physics,* **17:** 564, 1990.

Shalev, S., Leszczynski, K., Cosby, S., Chu, T. Treatment verification with portal films and on-line portal imaging. *Beijing International Congress on Medical Physics, May 1990.*

Shalev, S., Viggars, D.A. Software tools for the evaluation of volumetric treatment plans. *Beijing International Congress on Medical Physics, May 1990.*

Shalev, S. Recent advances in portal imaging. *Canadian Medical and Biological Engineering Society Meeting, Winnipeg, Canada, June 1990.*

Shalev, S., Chu, T., Cosby, S. Digital image processing for verification of radiotherapy treatment. *Canadian Medical and Biological Engineering Society Meeting, Winnipeg, Canada, June 1990.*

Shalev, S., Cosby, S., Leszczynski, K., Agbay, H. Dynamic on-line portal imaging with video-based systems. *ESTRO Annual Meeting, Montecatini, September 1990.*

Shalev, S., Viggars, D. Optimization of 3-D treatment plans. *ESTRO Annual Meeting, Montecatini, September 1990.*

Shalev, S. Portal verification and quality assurance. *ONCOVAIL, Vail, Colorado, March 1991.*

Shalev, S. 3-D treatment planning for conformal radiotherapy. *ONCOVAIL, Vail, Colorado, March 1991.*

Shalev, S. A critical review of 3-D treatment planning. *WESCAN Annual Meeting, March 1991.*

Shalev, S., Ding, X., Strachan, R., Ryder, S. The quantification of treatment accuracy. *ART91, Tumor Response Monitoring and Treatment Planning, Munich, April 1991.*

Shalev, S., Ryder, S., Cosby, S., Miskiewicz, K. Clinical experience with on-line portal imaging. *ART91, Tumor Response Monitoring and Treatment Planning, Munich, April 1991*

Shalev, S., Viggars, D., McCracken, D., Gatschuff, J. The limitations imposed on conformal treatment planning by patient movement and set-up errors. *ART91, Tumor Response Monitoring and Treatment Planning, Munich, April 1991.*

Viggars, D.A., Shalev, S. The clinical significance of patient motion and localization errors in radiotherapy. *Canadian Organization of Medical Physicists Meeting, Montreal, Canada, June 1990.*

Viggars, D.A., Shalev, S. Optimization of given dose in external beam radiotherapy using simple dose prescription. *AAPM Annual Meeting, St. Louis, July 1990.*

Wowk, B., Leszczynski, K., Shalev, S. Optimization ofmetal/phosphor screens for megavoltage imaging. *WESCAN Annual Meeting, March 1991.*

NURSING

Barbara Warren, *Director*
Kelly Filbert, *Secretary*

Nurses

Susan Bracken
Irene Chrunyk
Linda Friesen
Joann Kirbyson
Jan Lutz
Ellen Nelson
Linda Scott
Ines DeSousa, L.P.N.
Marlene Chambers
Bev Dodds
Nancy Johnson
Jeanette Kostenuik
Marion McCutcheon
Fran Sand
Jolene Tiegs-Fouillard
Sharon Kelly, L.P.N.

Clinical Assistants

Shelley Johnson
Carol Jones
Ishbel Turnbull
Lynn Jonasson
Ursula Merck

Unit Assistants

Maria Cabral, Mary Corden

Receptionists

Coleen Kelly, Michelle Powder

Nurses are a vital part of the care patients receive at the Manitoba Cancer Treatment and Research Foundation. In addition to providing direct nursing care, members of the department are instrumental in coordinating all services to patients during investigation, treatment and follow-up. In 1990, this meant actively planning and organizing for over 30,000 patient visits.

Nurses are available to patients to assist them with many aspects of their experiences with their illness and treatment. The main focus of nursing care is the patient's ability to continue to care for himself as much as possible. Nurses therefore teach patients self-care skills that will enable them to remain at home as much as possible through all phases of their illness. Nurses, of course, are also actively involved in assisting and supporting patients undergoing investigative procedures and in administering chemotherapeutic medications. Nurses are a strong source of support for patients and their families and are available to them not only during clinic visits but also by telephone between visits. The MCTRF nurses often form a strong liaison with nurses in the community who are providing home care.

In addition to direct patient care, nurses at MCTRF provide education and consultation to other nurses and health care professionals throughout the province. In 1990 fifty participants attended a 3-day workshop hosted by the Nursing Education Committee of MCTRF and St. Boniface hospital. They also prepared 3 nurses to administer cheotherapy in their respective outreach centers.

As the demand for quality care for people with cancer throughout the province increases, the nurses at MCTRF will be called upon to provide leadership and training to more and more nurses. They have developed expertise in cancer nursing and now must be prepared to share that expertise with others.

Requests for education from other centers are increasing and we need to plan a program to meet this growing need in a more organized fashion. The Director of Nursing was appointed to the University of Manitoba School of Nursing faculty in the fall of 1990 and this liaison will be instrumental in assisting us to promote oncology nursing education and research.

OUTREACH

Harvey Schipper, B.A.Sc., M.D. FRCPC, *Director*
Anne Nemecek, R.N., P.H.N., *Co-ordinator*
Cheryl Trylinski, *Data Manager*

Much interest in community-based cancer programs has been developing across Canada. This mounting interest was the catalyst for the first National Conference on Community-Based Cancer Programs held in Winnipeg October 12 - 14, 1990. The conference was planned by a committee of representatives of community-based (Outreach) cancer programs across Canada. The conference attracted 120 delegates who spent two days developing recommendations around patients' needs, quality of care and implementation steps for new communities' oncology programs. This conference will, hopefully, be the first of many opportunities for community-based cancer program representatives to come together.

One of the highlights of this October conference was the demonstration of the Manitoba Cancer Treatment and Research Foundation Computer Advisor System (Phase I). Over the past year, much work has been done to enhance this computer project. Outreach representatives were initially involved in deciding what information was needed in the system; and in July 1990, Brandon Outreach Center piloted the "beta" system of the Chemotherapy Advisor. Their input as a pilot centre helped the system developers to identify areas which would need further work. This computer advisor system will proceed to Phase II in 1991.

Outreach Symposium

In February 1990 the Outreach Symposium was held outside of Winnipeg for the first time. Eighty Outreach and Manitoba Cancer Treatment and Research Foundation staff met at Elkhorn Resort in the Riding Mountain National Park to exchange ideas, become more informed about cancer, and enjoy each others' company. It was decided that the Outreach Symposium would be hosed by one of the rural centers every other year.

Training/Orientation/Visits

One new physician for Dauphin Outreach received one month's orientation. This physician decided to do the orientation as part of his Family Practice Residency Program through Seven Oaks Hospital prior to moving to Dauphin to set up his medical practise. One nurse and one pharmacist were trained for the centres.

As in other years the Outreach administrative staff visited all centers.

Program Expansion

The Outreach Program is still in the expansion mode. Two new centers, Steinbach and Selkirk, will be working toward joining the program in 1991. To facilitate the process of planning, the Outreach administrative staff, with the help of the Planning Department at the St. Boniface General Hospital, have developed space guidelines for new centers. The necessity of developing these guidelines became evident when it was discovered that there were no guidelines available in Canada for appropriate chemotherapy spaces.

Other areas of program expansion include a move to integrate a formal psychosocial component into the Outreach Center programs. A proposal has been developed to link existing psychosocial community resources to Outreach Centers. Hopefully, there will be grant monies available to support a pilot project integrating these psychosocial supports.

Change and challenges for Outreach will continue into 1991. Cancer 2000, a National Task Force with provincial inputs, will likely provide recommendations directed at heightening the image of community oncology programs. The role study, being undertaken by Manitoba Cancer Treatment and Research Foundation as we move into planning for our new facility, will certainly identify some recommendations for Outreach. Our Outreach Advisory Committee has been dealing with issues which impact the direction of the Outreach Program. The recommendations from the first National Conference on Community-based Cancer Programs will provide challenges for our Manitoba program.

It is not without some trepidation that the Outreach Program moves in the 1990's. However, with the continued support of Manitoba Cancer Treatment and Research Foundation and St. Boniface General Hospital staff, as well as the commitment from the staff at work in the Outreach Centers, the Outreach Program will continue to provide safe cancer management to Manitoba's rural patients, and rise to the challenges of striving to do even better.

PEDIATRIC HEMATOLOGY/ONCOLOGY

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The year 1990 saw the recruitment of a co-ordinator for the Paediatric Bone Marrow Transplant Program, Dr. Jacek Winiarski. He has extensive experience with bone marrow transplants at the Huddinge Hospital in Stockhom, Sweden. Dr. Winiarski will be joining the Section in the summer of 1991 and will at that time begin the Pediatric Bone Marrow Transplant Program.

TABLE 1

Outpatients seen in the Pediatric Hematology/Oncology Clinic

TOTAL VISITS

Visits	New	Follow-up	Requiring Physician Participation
1978	126	1,560	1,756
1979	136	1,742	1,859
1980	107	1,582	1,688
1981	91	1,631	1,728
1982	149	1,858	2,007
1983	203	1,723	1,929
1984	197	1,943	2,140
1985	204	1,889	1,093
1986	223	2,057	2,290
1987	274	2,148	2,422
1988	266	2,367	2,633
1989	281	2,151	2,432
1990	**199**	**1,527**	**1,931**

For the latter half of 1990, Dr. M.L. Schroeder was on Sabbatical learning the skills in relation to the use of molecular biological techniques for HLA typing. Dr. Schroeder will be continuing on Sabbatical through to the end of June 1991.

Susan Powell, the social worker with our Pediatric Oncology group for many years, left during the summer of 1990 to take up a new position in British Columbia. Over the years, Susan was a moving force in organizing our adolescent group, and many other aspects of our psychosocial support program. Our new social worker, Kym Cuthill, brings with her considerable experience in dealing with oncology patients at St. Boniface Hospital.

The good news in the treatment of children's cancer is the striking improvement that has been made in decreasing mortality over the last thirty years. While the number of cancers in children has remained roughly constant during this period (see Table 2), the number of children dying from cancer has decreased dramatically from 251 between 1960 and 1969 to 86 between 1980 and 1989. This is remarkable progress, but we still have a long way to go. It also needs to be remembered that the more intensive treatment that we use now has increased the length of treatment and the side-effects.

TABLE 2

CANCER DIAGNOSIS AND MORTALITY

1959 - 1988

	No. of Children Age 0-14 Diagnosed With Cancer	No. of Children Age 0-14 Dying From Cancer
1959 - 1969	419	251
1970 - 1979	422	173
1980 - 1989	369	86

With more children with childhood cancers being cured and doing well, it has become critical to maintain the education and the psychological well-being of these children. To this end approximately 47 school visits were made to all parts of Manitoba to address a variety of issues including school re-entry after diagnosis or relapse, death education for classmates, or a discussion of physical and learning disabilities as a result of the treatment. These visits were supplemented by tours of the Hospital and the Cancer Foundation for the patients and classmates in seven instances, and by the seventh annual in-service day for educators held in November 1990. For the first time, a similar inservice day was also held in Brandon.

TABLE 3

HOME CARE FOR PEDIATRIC HEMATOLOGY/ONCOLOGY (1990)

No. of children with cancer	46
No. of children with hemophilia	10
No. of children receiving chelation therapy (anemias)	6
Total No. of Hematology/Oncology patients	62

Home care continues to be an important aspect of the care of children (Table 3). Home care services have been particularly important for the care of central lines/porto-caths, home parenteral nutrition, home chelation program for children with hemolytic anemia and for palliative care at home.

Much of the basic research by the members of the Section of Pediatric Hematology/Oncology is carried out at the Manitoba Institute of Cell Biology. Research reports of this activity are presented under the Manitoba Institute of Cell Biology report. Studies with significant clinical relevance are covered here. These studies are presented as I) Abstracts of published papers and II) Active Clinical Studies.

Abstracts of Published Papers

INHIBITION OF INTRAVASCULAR PLATELET AGGREGATION BY ENDOTHELIUM-DERIVED RELAXING FACTOR; REVERSAL BY RED BLOOD CELLS

D.S. Houston, R. Robinson, J.M. Gerrard

Studies were performed to determine whether endothelium-derived relaxing factor (EDRF) can inhibit platelet aggregation within the vascular lumen, and if so, whether the inhibition persists in the presence of red blood cells (RBCs). Canine femoral arteries mounted in an organ bath were perfused with physiologic saline solution to which acetylsalicylic acid was added to block prostacyclin formation. During contraction with phenylephrine, addition of acetylcholine to the perfusing solution to evoke EDRF release relaxed the vessel wall. Washed human platelets labelled with 14C-5-hydroxytryptamine were added to the perfusing solution, and activated by thrombin infused via a branch vessel. The perfusate was collected downstream and centrifuged, the fraction of 14C-5-hydroxytryptamine appearing in the supernatant reflected the degree of platelet activation. Stimulation of EDRF release with acetylcholine inhibited 14C-5-hydroxytryptamine release. Hemoglobin (Hb) (10-5 mol/L) blocked vascular relaxation and platelet-inhibition. RBCs at a hematocrit of 10% (treated with echothiophate to block erythrocyte cholinesterase) did not prevent relaxation but reversed the platelet inhibition. Lower hematocrits did not completely block the inhibition. Thus, erythrocyte Hb may modulate the inhibition of intraluminal platelet aggregation by EDRF.

STUDIES IN PATIENTS WITH BLEEDING DISORDERS SHOW THAT PLATELET-VESSEL INTERACTION IS IMPORTANT FOR THROMBOXANE FORMATION IN BLEEDING TIME WOUNDS

J.M. Gerrard, S. Singhroy, E. Duta, B. Nosek-Cenkowska, S.J. Israels, E.D. Israels

The production of thromboxane B2, the primary metabolite of thromboxane A2, and 6-keto prostaglandin F1, the primary metabolite of prostacyclin, were measured in response to a standardized vascular injury, the bleeding time, in patients with von Willebrand's disease and in patients with platelet function defects. Compared to controls, thromboxane B2 levels in bleeding time blood were significantly lower in subjects with von Willebrand's disease. In patients with platelet function defects associated with a deficient response to thromboxane A2, thromboxane B2 production in bleeding time blood was similar to controls. In subjects with other platelet function defects, thromboxane production was significantly lower than normal. 6-keto PGF1α production in bleeding time blood was not significantly different in patients compared to controls. The results suggest that bleeding time thromboxane production is influenced by the extent of platelet-vessel interaction.

EXPERT SYSTEM APPROACH TO ASSESSMENTS OF BLEEDING PREDISPOSITIONS IN TONSILLECTOMY/ ADENOIDECTOMY PATIENTS

N.J. Pizzi, J.M. Gerrard

The purpose of this expert system is to assess a predisposition to bleeding in a patient undergoing a tonsillectomy and/or adenoidectomy, as may occur with patients who have certain blood conditions such as hemophilia, von Willebrand's disease, and platelet function defects. This objective is achieved by establishing a correlation between the patients' responses to a medical questionnaire and the relative quantities of blood lost during their operation.

Three major modules constitute the system: the automated questionnaire to be completed by the patient, the expert system proper, and the patient database. The questionnaire is divided into fourteen sections on topics such as the occurrence of bruises and positive familial history. The expert system takes the responses to the questionnaire and determines risk categories for responses, personal data and the risk assessments generated by the expert system.

Subsequent to the development of the expert system prototype, inductive learning techniques were examined to automatically classify patients as either normal or abnormal. Specifically, Quinlan's ID3 induction algorithm was used whereby a training set of patient data generates a classification tree whose leaf nodes correspond to the classification outcomes.

This paper presents the architecture of the hematology expert system, identifies some problems encountered during the knowledge engineering process and presents some statistical data pertaining to the accuracy of its risk assessments. It also offers a comparative review of the expert system and inductive learning methodologies.

PLATELET STORAGE POOL DEFICIENCY: DIAGNOSIS IN PATIENTS WITH PROLONGED BLEEDING TIMES AND NORMAL PLATELET AGGREGATION

S.J. Israels, S. McNicol, C. Robertson, J.M. Gerrard

We evaluated 46 patients with prolonged bleeding times and no demonstrable abnormalities of either von Willebrand factor or platelet aggregation, for possible deficiency of platelet storage pool. Studies of ATP release from thrombin-stimulated platelets and enumeration of dense granules in platelet whole mounts were performed in these patients. Seventeen patients (35%) had both decreased ATP release and decreased numbers of dense granules, suggesting the presence of a storage pool defect. Thus, storage pool deficiency may be present in the absence of the classical aggregation abnormalities. Evidence of storage pool deficiency should be considered in all patients with an isolated unexplained prolongation of the bleeding time. The methods used in this study are readily applicable to most clinical laboratories.

DEFICIENT COLLAGEN-INDUCED ACTIVATION IN THE NEWBORN PLATELET

S.J. Israels, M. Daniels, E.M. McMillan

We have investigated the impaired secretion response of neonatal platelets. We compared the response of washed neonatal and adult platelets to thrombin and collagen, and to specific activators of calcium flux (inositol trisphosphate) and protein kinase C activation (oleoyl-acetyl glycerol). Neonatal platelets show no impairment of aggregation, secretion of [14C] serotonin or phosphorylation of specific intracellular proteins in response to thrombin, inositol trisphosphate, or oleoyl-acetyl glycerol. However, neonatal platelets have a markedly decreased response to collagen. To further evaluate this deficient response, we examined specific aspects of the collagen activation pathway. Collagen-platelet interaction as measured by adhesion of platelets to collagen-coated dishes showed no difference in adhesion of neonatal platelets compared to adult controls (10.2 + 11.6 versus 18.6 + 9.3%). The presence of GPIa/11a, a Mg2+-dependent collagen receptor, was evaluated by flow cytometric analysis of binding of fluorescein-tagged monoclonal antibody, 6F1 (directed against GPIa/IIa). There was no difference either in the percent of platelets that bound antibody (80 versus 81%) or in the mean fluorescence intensity of the adult and neonatal samples. Phosphoinositide hydrolysis was decreased in neonatal platelets in response to collagen but normal in response to thrombin. Neonatal platelets released more arachidonic acid than adult platelets in response to thrombin (29.5 + 3.2 versus 19.6 + 1.8%) but less than adult platelets in response to 10 ug/mL collagen (3.2 + 1.1 versus 9.3 + 3.0%). Thromboxane B2 production was also decreased in response to collagen (52.7 + 12.6 versus 101.4 + 18.7 ng/Ml). These results suggest that the deficient collagen response in neonatal platelets may lie in transduction of the collagen signal to phospholipases A2 and C. (Pediatr Res 27:337-343, 1990)

Active Clinical Studies

CANADIAN MULTICENTRE TRIAL OF CHILDHOOD LEUKEMIA AND LOW FREQUENCY ELECTROMAGNETIC FIELD EXPOSURE

Leukemia is the most common childhood malignancy in Canada. The etiology of leukemia is not well understood and several recent studies have suggested that children exposed to strong low frequency electrical or magnetic fields may be at higher risk of this cancer.

Previous studies, however, have suffered from two substantial limitations: inability to accurately quantify electromagnetic field exposure, and lack of sufficient numbers to adequately determine any relationship among different subtypes of leukemia.

The risk of all childhood leukemia and each subtype of leukemia in the presence of 60 hertz electromagnetic field exposure will be examined using the following criteria:

a) indirect measurement of electromagnetic field (EMF) exposure in current and all previous residences, using wire configuration data.

b) exposure to 60 hertz magnetic and electrical field as measured by 24 hour dosimetry of the child's bedroom in the first year of life. This measurement will be taken on a subset of the total study cohort, depending on availability. Average exposure, duration of high exposure, and various components of electromagnetic field exposure can be analyzed separately from this data.

c) exposure to 60 hertz magnetic and electrical field as measured by personal dosimetry on a 48 hour basis. This measurement will be restricted to subjects still alive at time of data collection.

As well, we will assess the possible association of the following groups of factors with total childhood leukemias, and each leukemia subtype: family history of cancer and congenital anomalies;

parental occupational and recreational exposures, from the year prior to the birth of the subject to the time of diagnosis; gestational factors and other exposures surrounding pregnancy; post-natal factors, including radiation, and exposure to viral infections, chemicals, and medications; and socio-economic status.

A total of 400 parents of children with leukemia will be interviewed with a standardized questionnaire, along with an equal number of control parents with children of the same sex matched for year of birth. All interviews will be conducted when the case children's disease is in remission.

CCG-7881 - EVALUATION OF VINCRISTINE, ADRIAMYCIN, CYCLOPHOSPHAMIDE AND ACTINOMYCIN, WITH OR WITHOUT THE ADDITION OF IFOSFAMIDE AND ETOPOSIDE IN THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSISED EWING'S SARCOMA OR PRIMITIVE NEUROECTODERMAL TUMOUR OR BONE. A PHASE III INTERGROUP STUDY

In this study a control regimen of high dose intermittent pulses of vincristine, adriamycin and cyclophosphamide (VAC) is compared with an experimental regimen using courses of ifosfamide and etoposide, alternating with VAC. In both regimens adriamycin is replaced with actinomycin-D, when the total cumulative dose of adriamycin reaches 375 mg/M2 in order to prevent anthracycline-induced cardiotoxicity. In both regimens, local therapy includes intensive radiation therapy to a total dose of 5580 cGy using 31 fractions of 180 cGy/fraction.

CCG-631 - THE INTERGROUP RHABDOMYOSARCOMA STUDY III

The IRS III study is based on the results obtained from the IRS I and II studies. Patients with favourable histology group I tumours will receive cyclic sequential vincristine and actinomycin-D with no radiation. Patients with group I or II unfavourable histology will receive vincristine, adriamycin, cis-platinum, cyclophosphamide induction and pulse-VACdC, alternating with pulse-VAC maintenance. Radiation to the tumour bed will also be administered to unfavourable histology patients. Patients with group II favourable histology will be randomized to receive cyclic-sequential vincristine and actinomycin-D with or without adriamycin; all patients to receive radiation to the tumour bed. Patients with group II or III tumours involving the orbit or non-parameningeal sites of the head will not be randomized, but will receive local radiation and cyclic-sequential vincristine, actinomycin-D only. Patients with group III and group IV tumours will be randomized to receive an induction chemotherapy with pulse-VAC or two experimental arms containing vincristine, actinomycin-D, cyclophospamide, cis-platinum, adriamycin + VP-16. Additional strategies for group III and IV patients will include second and third look surgeries and non-cross-resistant intensification therapies with adriamycin/DTIC, high dose actinomycin-D/VP-16, or high dose actinomycin-D/DTIC. Patients with primary parameningeal sites will have their cranial prophylaxis stratified according to the potential risk of CNS extension. Patients with genitourinary primaries will receive intensive primary chemotherapy and delayed radiation and surgery in an attempt to decrease therapy-related morbidity.

CCG-671 - RHABDOMYOSARCOMA STUDY IV, PILOT STUDY FOR CLINICAL GROUP III DISEASE

The IRS-IV pilot proposes to treat patients with ifosfamide, actinomycin-D and vincristine, followed by hyperfractionated radiation therapy, followed by a maintenance therapy with ifosfamide, actinomycin-D and vincristine. Assuming that the results of the pilot study are acceptable, the IRS-IV stage III randomized study will proceed. Patients will be randomized between three chemotherapy arms, including vincristine, actinomycin-D and cyclophosphamide; vincristine, actinomycin-D, ifosfamide; and vincristine, etoposide and ifosfamide. Patients will also be randomized to receive standard radiation therapy to a total dose of approximately 5,000 Cgy, or hyperfractionated radiation therapy to a total dose of approximately 6,000 Cgy.

CCG-6881 - INTERGROUP RHABDOMYOSARCOMA STUDY IV PILOT STUDY FOR CLINICAL GROUP IV DISEASE

As accrual on IRS-III has exceeded expectations, patients with Stage IV disease will be closed to further patient entry on this protocol. The IRS committee has therefore recommended enrolment of Stage IV patients henceforth on a pilot study which will be used in the development of the forthcoming open, randomized IRS-IV trial. This IRS-IV pilot study for stage IV disease is based on the known poor outcome for this group of patients (long term disease-free survival of 20-27%), as well as a number of new developments in the treatment of soft tissue sarcomas. These developments include the "discovery" of ifosfamide and of melphalan as effective agents in the treatment of soft tissue sarcomas and the recognition that hyperfractionated radiation therapy may provide better local disease control than standard radiation therapy. The IRS-IV, stage IV pilot will treat patients with the combination of vincristine, doxorubicin and ifosfamide. After an initial induction phase, patients will receive hyperfractionated radiation therapy, followed by a maintenance with alternating courses of vincristine, ifosfamide, doxorubicin and subsequently vincristine, actinomycin-D, cyclophosphamide (VAC). For patients who do not show an initial favourable response to the vincristine, ifosfamide, doxorubicin combination, cross-over to vincristine, actinomycin-D, cyclophosphamide will take place.

The IRS-IV, stage IV pilot study, if acceptable with regard to disease response and toxicity will then be expanded into a group-wide randomized trial. The trial will compare vincristine, ifosfamide, doxorubicin and vincristine, melphalan with vincristine, ifosfamide, etoposide. This study will also be randomized to standard versus hyperfractionated radiation therapy. The vincristine, ifosfamide, doxorubicin combination has been already piloted by the St. Jude's group, and because the vincristine, ifosfamide, etoposide combination is to be piloted concurrently for patients with stage III disease (CCG-671), in both the pilot and the open study patients who do not respond to initial therapy will be assigned to treatment with standard vincristine, actinomycin-D and cyclophosphamide (VAC). This will provide information concerning cross-resistance between the three experimental induction therapies and VAC standard induction therapy.

PROTOCOL NWTS-4

The NWTS-4 hopes to further refine the treatment for patients with Wilms tumour. The two main questions include whether Actinomycin-D, when administered in a 'pulse-intensive' fashion will be superior to the five day approach. Clearly, the pulse-intensive therapy will be more convenient for the patients, but more importantly, should have some theoretical benefit because of its increased intensity. The length of therapy required for the various stages and histological subtypes will also be further refined. It is hoped that the NWTS-4 will define the "state of the art" treatment for patients with Wilms tumour, and in this respect, is a very important study. The question of ideal therapy for patients with the "rhabdoid tumour" and patients with stage II, III and IV anaplastic tumours, of course, will not be defined by this study, but hopefully some information regarding optimal treatment for these patients will still emerge from on-going accrual on NWTS-3.

CCG-321P1 - INTENSIVE MULTI-MODAL THERAPY AND BONE MARROW TRANSPLANTATION FOR NEWLY DIAGNOSED STAGE IV, AND POOR RISK STAGE III NEUROBLASTOMA PATIENTS, PHASE III STUDY.

For all tumours studied to date, bone marrow transplantation has been most successful when performed at a time of minimal tumour burden prior to disease progression. For this reason, treatment with standard chemotherapy will be administered at three week intervals for four courses from the time of initial diagnosis (weeks 0, 3, 6 and 9). This will be followed by a second look surgical procedure to remove any gross residual disease, followed immediately by local irradiation to residual unresectable tumour sites. This cytoreductive regime will then be followed shortly thereafter by intensive non-cross-resistant chemotherapy and bone marrow transplantation. The induction chemotherapy that will be used will be the standard therapy that has been used for neuroblastoma for the past ten years with cyclophosphamide, vincristine and DTIC. With this therapy, maximal responses are usually obtained by weeks 10-13, i.e., after the fourth or fifth courses of chemotherapy. Further benefit has not been demonstrated by continuing this therapy for a longer period of time; in fact, tumour progression has been observed in 15, 25, 40 and 50% of patients by 9, 12, 15 and 22 weeks, respectively. Therefore, after the first four courses of chemotherapy, second-look surgery and local irradiation will be performed at week 11, with transplantation at week 13.

The CCG-321P1 protocol is only available for patients who have an HLA-compatible sibling donor. Patients who do not have a donor will, therefore, be treated on an analogous protocol using repeated cycles of less intensive chemotherapy without transplantation (CCG-321P2).

CCG-3881 - BIOLOGY AND THERAPY OF GOOD, INTERMEDIATE, AND SELECTED POOR PROGNOSIS NEUROBLASTOMA

Four groups of patients with neuroblastoma are to be defined and treated according to the following protocols.

Patients with stages I and II disease and less than three copies N-myc will be treated with surgery alone, unless there is symptomatic cord compression, in which case, children with rapidly progressive neurologic defects are to be treated with surgery with the possible addition of radiation therapy in lesions of a more chronic unstable nature.

Patients with stage II, III and IV and unfavourable prognostic signs will be treated on other protocols. This will include patients who are stage II greater than one year of age and have greater than or equal to three copies of N-myc, patients with stage III greater than one year of age and unfavourable histopathology, greater than or equal to three copies of N-myc or elevated ferritin, and patients with stage IV who are greater than one year of age.

For the patients with stages II with greater than or equal to three copies of N-myc and patients with stages III and IV who are to be treated under the current protocol, following diagnostic biopsy or subtotal tumour resection, they will receive a 120-day induction phase of chemotherapy consisting of cyclophosphamide, cisplatinum, adriamycin and VP-16 (constant infusion). At day 120, patients are evaluated for delayed surgery. An attempt will be made to resect previously unresectable tumour or to debulk residual disease. Radiation therapy is given to tumours that do not appear to be amenable to surgical debulking, as well as to tumour persisting after surgery. Following completion of radiation therapy, patients are to be given a 113-day course of chemotherapy, utilizing the same agents as those used in the induction phase. Patients with residual disease remaining after surgery at day 120, are surgically explored and metastatic foci biopsied to determine whether or not active disease is present. Patients having no evidence of disease are observed without further therapy, while those who have histologic evidence of persistent disease go on to alternate therapy.

CCSG-921 - PROTOCOL FOR THE TREATMENT OF UNFAVOURABLE MEDULLOBLASTOMA AND INTERCRANIAL PRIMITIVE NEUROECTODERMAL TUMOURS (PNET), MALIGNANT EPENDYMOMA, EPENDYMOMABLASTOMA, PINEOBLASTOMA, AND CENTRAL NEUROBLASTOMA, A PHASE III

MULTI-INSTITUTIONAL STUDY

The proposed CCG-921 study is based on favourable results obtained in the previous CCG-942 study, as well as the very exciting preliminary data obtained from the "8 in 1" pilot program. The study call for a randomization between the chemotherapy-containing arm of the CCG-942 using the three drugs, CCNU, vincristine and prednisone, and the "8 in 1" program. Radiation therapy is to be standardized in both treatment arms. In the control arm vincristine is administered weekly during the radiation therapy phase and maintenance chemotherapy follows the radiation therapy for approximately one year. In the "8 in 1" arm, two courses of "8 in 1" are administered prior to radiation therapy and eight courses are administered after radiation therapy.

CCG-1891 - TREATMENT OF NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN WITH AN INTERMEDIATE PROGNOSIS*

Regimen A - This regimen, a standard therapy, is based on preliminary results from the previous Children's Cancer Study Group study (CCG-105) in which patients will receive induction therapy including Vincristine, Prednisone, L-Asparaginase and intrathecal Methotrexate, Vincristine, and Prednisone for four weeks. Consolidation is followed by interim maintenance I of four weeks' treatment with 6-Mercaptopurine, Methotrexate, Vincristine and Prednisone and then eight weeks of delayed intensification including Vincristine, Dexamethasone, Adriamycin, L-Asparaginase, Cyclophosphamide, Cytosine Arabinoside, 6-Thioguaine and intrathecal Methotrexate. Up to this point, all regimens are identical. It is at this point that differences in the three regimens begin. In regimen A, maintenance therapy will be Vincristine and Prednisone every 28-days combined with daily 6-Mercaptopurine and Methotrexate together with intrathecal Methotrexate once every 12-weeks. Maintenance therapy will continue for 88-weeks for girls and for 140 weeks for boys.

Regimen B - Regimen B is identical to regimen A to the end of the delayed intensification. At this point, children enrolled in regimen B will receive 8-weeks of interim maintenance with 6-Mercaptopurine, Methotrexate, Vincristine and Prednisone followed by and 8-week delayed intensification repeat using Vincristine, Dexamethazone, Adriamycin, L-Asparaginase, Cyclophosphamide, Cytosine Arabinoside, 6-Thioguaine and intrathecal Methotrexate. After the delayed intensification, children will receive maintenance with Vincristine and Prednisone every 28-days together with daily 7-Mercaptopurine and Methotrexate, and intrathecal Methotrexate every 12-weeks. This maintenance will go for 72 weeks in girls and 124 weeks in boys before therapy is discontinued.

Regimen C - This third regimen, regimen C, is similar to regimen A in that Vincristine and Prednisone are to be used, but they are to be given every 21-days instead of every 28-days. 6-Mercaptopurine and Methotrexate are to be given daily and intrathecal Methotrexate is to be given once every 12-weeks as in regimen A.

Below, very briefly, the rationale for the variations chosen in the standard therapy are as follows:

Regimen B attempts to evaluate whether a second delayed intensification is superior to a single one. Regimen C attempts to determine whether Vincristine and Prednisone given on a 21-day schedule is superior to Vincristine and Prednisone given on a 28-day schedule.

*(In patients aged 1-2 years with white blood counts <100,000/ul, patients aged 1-10 years inclusive with white blood counts of 10,000 to 50,000/ul, and boys aged 1-10 with white blood counts of <10,000/ul and platelets of <100,000/ul, excluding patients with lymphoma-leukemia and/or L3 morphology).

CCG-1881 - TREATMENT OF NEWLY DIAGNOSED LOW RISK ACUTE LYMPHOBLASTIC LEUKEMIA. A PHASE III GROUP WIDE STUDY.

To summarize, this study will attempt to determine whether the addition of a delayed intensification therapy will improve the outlook for children with low risk acute lymphocytic leukemia. Intensive therapy would potentially be associated with approximately a 2% mortality; however, with between 15 and 20% of patients relapsing on current therapy, this seems to be a reasonable trade-off if the therapy is effective.

CCG-1882 - TREATMENT OF NEWLY DIAGNOSED ACUTE LYMPHOCYTIC LEUKEMIA IN CHILDREN WITH A POOR PROGNOSIS EXCLUDING INFANTS AND PATIENTS WITH LYMPHOMA OF FAB L3 BLASTS. A PHASE III GROUP WIDE STUDY

This study will attempt to:

a) Determine that patients showing a good response by day 7 of chemotherapy, with BFM without cranial RT will show decreased morbidity without an alteration in event free survival when compared with standard BFM.

b) Improve even t free survival of those children treated with BFM showing a poor response on day 7 by treating them with intensified chemotherapy with minimal increase in toxicity.

c) Further study the interaction of transitional prognostic factors; day 7 marrow response, cytogenetics, and immunophenotype on outcome.

CCG-1883 - TREATMENT OF NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA IN INFANTS LESS THAN 12 MONTHS OF AGE. A PHASE III GROUP WIDE STUDY.

To summarize, CCG-1883 will build on the encouraging results of CCG-107. It is a non-randomized study, which will have the following features:

1. Intensive four-drug induction.
2. Consolidation with high-dose Ara-C and L-asparaginase, as well as very high dose methotrexate with leucovorin rescue and intrathecal chemotherapy.
3. Interim maintenance regimen with vincristine, moderate dose methotrexate and L-asparaginase (Capizzi 1).
4. Delayed intensification therapy, which, in fact, is a truncated version of the induction and consolidation, and based on the theoretical principles delineated by the BFM protocol.
5. "Standard" maintenance therapy.

A very significant feature of this protocol will be the prospective performance of psychoneurologic testing to confirm the initial impression that by eliminating central nervous system radiation, long term CHS sequelae have been reduced, or perhaps even eliminated.

CCG-2891 - TREATMENT OF CHILDREN <21-YEARS OF AGE WITH NEWLY DIAGNOSED ACUTE NON-LYMPHOCYTIC LEUKEMIA (ANLL) AND MYELODYSPASTIC SYNDROME (MDS)

There are two major questions being asked in CCG-2891. These are:

1) Can one improve both remission induction, as well as long term survival by intensify ing induction drugs, especially timing of chemotherapy given without untoward toxicity?

2) Can similar results found after allogenic bone marrow transplantation be obtained using autologous bone marrow rescue with potentially less toxicity, as suggested by European investigators?

CCG-E13 - CASE CONTROL STUDY OF HODGKIN'S DISEASE IN CHILDHOOD

This is a case control interview study of children with Hodgkin's disease to evaluate previously hypothesized risk factors and to generate new ones. On the basis of epidemiological findings, Hodgkin's disease appears to be three diseases - a childhood disease (affecting those in the age group 0-14 years), a young adult disease (15-44 years), and an older adult disease (usually 55+ years). This study focuses on the childhood form of the disease and will attempt to:

a) test a major hypothesis that children with Hodgkin's disease have different patterns of infectious disease than do matched controls;
b) evaluate parental occupational exposures as risk factors for childhood Hodgkin's disease;
c) evaluate environmental exposures to wood and chemicals as possible risk factor in children;
d) evaluate familial aggregation of Hodgkin's disease;
e) evaluate risk factors for childhood Hodgkin's disease separately for histological subtypes of the disease and by disease stage and age at diagnosis; and
f) collect serosamples for use in future biological studies.

CCG-E15 - CASE CONTROL STUDY OF ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common form of malignancy in children under 15 years of age, and the incidence of leukemia appears to be increasing. The present study is designed to examine the role of risk factors for childhood ALL within biologically defined subgroups (i.e. immunophenotyping, morphologic classifications, and karyotypic analysis of diagnostic bone marrow samples). This study will assess whether biologically or clinically distinct subgroups of ALL are also etiologically distinct.

CCG-0892 - A PHASE II TRIAL OF HUMAN RECOMBINANT IL-2 GIVEN AS A FOUR-DAY CONTINUOUS INFUSION FOR CHILDREN WITH REFRACTORY NEUROBLASTOMA, NON-HODGKIN'S LYMPHOMA, OR SARCOMAS

This is a phase II study designed to determine the anti-tumour effect of IL-2, a single agent therapy for pediatric oncology patients. Because of the IL-2 induced responses observed for adults with melanoma, renal cell carcinoma and lymphoma, it is possible that pediatric neuroblastoma and lymphoma may potentially have similar susceptibility to this immunologic approach. In vitro data have documented the susceptibility of neuroblastoma cell lines and non-Hodgkin's lymphoma cells to in vitro destruction by IL-2 activated peripheral blood lymphocytes. Separate studies show the susceptibility of pediatric sarcoma cell lines to in vitro lymphocyte-activated killer cell mediated destruction. This trial will therefore focus on neuroblastoma, lymphoma and sarcoma patients.

CCG-L891 - RETROSPECTIVE COHORT STUDY OF LATE EFFECTS IN LONG TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

The study population will include all patients entered on front line CCSG Studies who are at least 18 years old and who have been in continuous complete remission. (There are approximately 1400 eligible patients.) Survivors will be traced and an introductory letter will be sent to each patient with address correction requested in the mailing envelope. The complete list with address corrections will be sent to the telephone centre for contact or for further tracing where necessary. This will be followed by a telephone interview which will average approximately 45 minutes. The relatively few respondents who have a child with a birth defect will be asked a series of questions relating to possible confounding variables which may take an additional 20 minutes. The interview is to cover demographic questions and focus on respondents' health, fertility, the health of their children, risk taking behaviour, self-image and depression. In the instances of second cancers and for children with birth defects, permission to seek medical records will be requested.

CCG-1901 - TREATMENT OF NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN WITH MULTIPLE UNFAVOURABLE PRESENTING FEATURES EXCLUDING INFANTS AND FAB L3 BLASTS

Children with acute lymphoblastic leukemia are divided by the Children's Cancer Study Group into several categories based on their likelihood and pattern of relapse. In the previous study to the present one (CCG-123) a subset of children aged ≥ 1 year with lymphomatous features, specifically massive splenomegally, massive lymphadenopathy, and/or a large mediastinal mass together with a WBC ≥ 50,000/ul, Hgb ≥ 10 g/dl, and/or T-cell ALL by E-rosette or monoclonal antibody. Seventy-five percent of this population is E-rosette positive. On CCG trials before 1981, this group had a 3-year disease free survival of 40% with an actuarial rate of CNS and testicular relapse of 10% and 20%. In the most recent groups entered into CCG-123, for regimens A and D, individuals entered after December 1985 the two year event free survival has been 70% and 90% in the two regimens respectively.

In the present study, children aged one to twenty years inclusive with acute lymphoblastic leukemia or undifferentiated leukemia, who have at least one of either:

A) An initial WBC ≥ 50,000 ul,
B) Hgb ≥ g/dl, or
C) T-cell ALL by E-rosettes or greater than 20% positivity for monoclonal antibodies 9.6, 35.1, OKT11 in the diagnostic bone marrows blasts,

and at least one of the following three criteria.

A) massive lyphadenopathy, or
B) massive splenomagaly, or
C) large mediastinal mass

and do not have FAB L3 leukemia cell morphology.

As an additional study entry criteron, patients must not have had previous therapy for acute leukemia, except for emergency therapy for blast cell crisis, superior vena cava syndrome or renal failure due to leukemic infiltration of the kidneys, and any such therapy must not include more than twenty four hours of steroids prior to initiation of the protocol.

CCG-BP903 - CHILDHOOD CANCER GENETICS

Current estimates suggest that up to 10% of children with cancer may have a genetic or familial contribution to the disease. The purpose of this study is to identify such children, to obtain pedigree information in a consistent fashion on such families, to apply segregation analysis for family pedigrees to detect family aggregates and inheritancy patterns and to identify patients of particular interest for further laboratory study.

THE USE OF HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN IN THE PROPHYLAXIS AND TREATMENT OF NEONATAL AUTOIMMUNE THROMBOCYTOPENIA

Most infants with neonatal autoimmune thrombocytopenia do well with resolution of their thrombocytopenia as the level of passively acquired maternal autoantibodies decline. However, in a small number of infants serious haemorrhage can occur during the period of thrombocytopenia. Intracranial or other serious haemorrhage occurs in up to 4% of infants with neonatal autoimmune thrombocytopenia and therefore prompts therapy in infants with platelets <50 x 10^9/L. The specific aims of this study are three;

1. To determine the benefit of maternally administered high dose intravenous immunoglobulin in the prevention of fetal thrombocytopenia following pregnancies at risk of neonatal autoimmune thrombocytopenia.

2. To determine the platelet response to high dose IVIG in newborn infants with neonatal

autoimmune thrombocytopenia and platelet counts <50 x 10^9/L.

3. To determine whether the frequency of thrombocytopenia correlates with the presence or titer of circulating maternal auto antibody to specific platelet glycoproteins.

The infant will be treated again with the same dose of IVIG if the platelet count again falls below 50. If after the first infusion of IVIG the platelet count remains below 50 the infant will receive a second dose of IVIG 1.0G/kg. 24 hours later platelet counts will be checked again. If the platelet count is now over 50 the infant will be observed. If the platelet count is still less the 50 a third dose of IVIG will be given in association with IV methylprednisone 3 mg/kg. If the platelet count remains below 50 following this therapy the infant is off study and further treatment is at the discretion of the physician. Laboratory studies that would be obtained in addition to platelet counts would include maternal platelet count and maternal serum and platelets for platelet antibody studies, as well as an ultrasound of the infant's head at the time of entry. Following therapy platelet counts will be followed on a weekly basis for 12 weeks.

PHARMACY

Venetia Bourrier, B.Sc. Pharm., *Director*

Organization

In the year 1990, a newly defined Department of Pharmacy was established. The activities performed by the Director and developments which occurred during the past year are highlighted below.

Intravenous (IV) Admixture Service

Efforts were made to achieve last years' goal whereby the Department of Pharmaceutical Services at the Health Sciences Centre would provide complete coverage of the antineoplastic admixture service to the Manitoba Cancer Treatment and Research Foundation. In the upcoming year, the program will be expanded and the goal achieved.

Clinical Pharmacy Services

A clinical pharmacy service was established at the Manitoba Cancer Treatment and Research Foundation. Patient Education in the form of drug counselling was performed on a consultation basis in both the chemotherapy and radiotherapy areas. An Oncology Pharmacy Newsletter was developed and circulated with the Outreach Newsletter. Participation in the Brain Tumor Clinic multidisciplinary team meeting was continued. The goal for the upcoming year is to expand the clinical pharmacy service to include more staff education via inservicing.

Research

Activities performed in the Clinical Investigations Office included procurement of various study medications, review of the pharmaceutical data in new protocols and preparation of drug data information sheets for Clinical Investigation Office and nursing staff. Pre-printed Drug Order Forms were created for specific studies conducted in Brain Tumor Clinic. The Director continued to be a liaison with the Clinical Investigations pharmacist at Health Sciences Centre.

The Outreach Program

Site visits to monitor existing pharmacy standards were made to Dauphin, Gimli and Brandon. A presentation on the Outreach program was also made in Russell, Swan River and Selkirk.

Training and continuing education involving the Outreach pharmacists were continued.

The Quality Assurance program draft was circulated to the Outreach centres for field testing.

Audits of the Quality Assurance program criteria will be continued in conjunction with the site visits.

In an effort to improve the acquisition of antineoplastic drugs by the Outreach centres, drug inventory lists of all the centres were circulated.

Future Planning

A Role Statement delineating the needs for a Pharmacy Department in the proposed new cancer facility was developed. The goal for the upcoming year is the completion of the Functional Program.

PLANNING

Janet Bjornson, *Director* (effective March 1991)
Judy Watts, *Project Coordinator*
Dianne Lamontagne, *Administrative Assistant*

The Planning Department of the Foundation was established and staffed in 1990.

The primary purpose of this department is to oversee planning and development of the expansion and redevelopment project of the Foundation.

The first step in the planning process was to develop a Role Statement. The Role Statement, which identifies current programs, programs to be expanded, and new programs, provides the basis for negotiation with government on the scope and parameters of the capital program.

The Role Statement document was prepared with extensive input from department heads and coordinated by senior administration. It provided an opportunity to reexamine legislation, mission, current programs, and to develop a vision for the future. The Planning Department is currently in the process of negotiating the Role Statement with government and is actively preparing for the next project stage: development of the functional program.

The future appears both challenging and exciting as the Planning group work with staff of the Foundation to develop the commitment to a capital redevelopment of a comprehensive cancer centre that will provide the citizens of Manitoba with strong and innovative programs for cancer care.

PSYCHIATRIC ONCOLOGY SERVICE

Harvey Chochinov, M.D., FRCPC, *Head*

The Psychiatric Oncology Service, designed specifically to meet the needs of the Manitoba Cancer Treatment and Research Foundation, began in September, 1987. Up until then, patients requiring psychiatric consultation were referred to the Department of Psychiatry's general Consultation Liaison (C/L) Service if in hospital, while no formal readily available channel existed for outpatient psychiatric consultation. While psychiatric oncology falls within the discipline of the C/L Psychiatry, it does require specific skills. These include psychiatric aspects of symptom control, familiarity with emotional issues related to life-threatening and terminal illness and bereavement, and ability to diagnose and manage a variety of psychiatric syndromes in the context of malignant disease.

Inpatient and outpatient psychiatric consultation (along with follow-up when necessary) is available to any Cancer Foundation affiliated physician. While consultations are often initiated by other Foundation professional staff, all referrals must be made with the explicit approval of the attending physician. Supervision is available to all Foundation clinical staff with respect to emotional aspects of patient management. Since August, 1989, psychiatric residents doing their C/L rotation have had the opportunity to participate in this service; this has consisted of clinical exposure, evaluation and management of psychiatric problems in patients with malignant diseases.

Staff support services include informal as well as formal psychiatric consultation for any Cancer Foundation employee. Weekly psychosocial rounds provide a forum open to the multidisciplinary ward staff, facilitating discussion and interchange on emotional aspects of patient management.

Our current research includes a project entitled "Depression and the Desire For Death Among the Terminally Ill" supported by grants from the Manitoba Cancer Treatment and Research Foundation and The Manitoba Mental Health Research Foundation. A second project, entitled "Stimulants for Depression in the Terminally Ill" was recently funded by a grant from the Manitoba Research Council.

1990 Statistics:

Outpatient Consultations	20
Inpatient Consultations	55
Outpatient Follow-Up Visits	192
Inpatient Follow-Up Visits	81

RADIATION ONCOLOGY

E. Baral, M.D., Ph.D, *Acting Director*
C. Campbell, K. Filbert, *Department Secretaries*

Radiation Oncologists

P.A. Blood, B.M., FRCPC
S. El-Sayed, M.B., B.Ch., FFR, FRCR
P. Hahn, M.D., Ph.D.
K.D. Jones, M.B., B.Ch., FRCS (ENG.), FRCR
S. Larsson, M.B., Ch.B., FRCR
K. Vijayaraghavan, M.B., B.S.

Residents

R.N. Gramatovici, M.D.
A. Leylek, M.D.
A. Ilnyckyj, M.D.
T. Corbett, M.D.
J.N. Aronowitz, M.D.

Technologists

Joan Howes, *Supervisor*

Deb Bettig
Tannis Engel
Jacquie Grestoni
Darren Hughesman
Susan Johnson
Gina Kowaski
Pam Thomson
Deb Bridle
Joan Friess
Julie Halfdanson
Karen-Ann Johnson
Heather Jory
Tracy Maciboric
Karen Wedlake

Joe Pellittiere, Rose Villabrille, *Unit Assistants*
Angeline Pope, *Receptionist*

Therapy Equipment

M.R. MacCharles Unit:

Therac 40 Sagittaire linear accelerator
Siemens KD-2 linear accelerator
6 MV S.H.M. linear accelerator
A.E.C.L. Model F. Cobalt beam therapy unit
250 kV x-ray therapy unit
140 kV x-ray therapy unit
Picker simulator
A.E.C.L. Therasim 750 simulator
A.E.C.L. Theraplan treatment planning computer
TAG<ED 2450 MHz hyperthermia unit

St. Boniface General Hospital Unit:

100 kV superficial x-ray therapy unit
A.E.C.L. Theratron 780 Cobalt unit
Picker simulator

External Irradiation

At the M.R. MacCharles Unit, **1283** new patients were treated and **328** patients were retreated.

At the St. Boniface General Hospital Radiation Oncology Unit, **560** new patients were treated and **158** were retreated.

The Department of Radiation Oncology is represented at both the M.R. MacCharles Unit and the St. Boniface Hospital Oncology Unit.

The consultative therapeutic services are provided at the M.R. MacCharles Unit, at which the major equipment facilities are located, but a significant number of radiation oncology consultations and radiotherapeutic interventions are provided at the St. Boniface Hospital Oncology Unit where an isocentric telecobalt unit and simulator facility are available. A co-ordinated multispecialty oncology program, including integrated radiation oncology and medical oncology clinics at St. Boniface Hospital is being established, which necessitated the introduction of the complete state-of-the-art radiotherapeutic equipment. Accordingly, the St. Boniface Radiation Oncology Unit will be expanded by the addition of a dual energy linear accelerator and the establishment of an infrastructure including Medical Physics, Treatment Planning and Mould Room during the year 1992.

The prime objective of the Department of Radiation Oncology is to provide exemplary patient care and optimal radiation treatment for cancer patients in Manitoba. Planning of radiation treatment has become increasingly sophisticated and the computerized treatment planning system underwent an extensive upgrade with the new technique of 3-dimensional treatment planning using software partly developed in the Department of Physics.

Also, an on-line portal imaging system, one of the first and certainly one of the best of its kind, was developed in the Department of Medical Physics and has been installed on the KD-2 linear accelerator for clinical evaluation.

In order to keep the waiting times for treatment within reasonable limits, the working hours for the high energy linear accelerator had to remain extended. The radiation therapy technologists, physicists and the radiation oncology consultants have all generously given their time and support to maintain our clinical services at as optimal a level as was possible, considering the availability of relatively limited resources.

All department members have major undergraduate and postgraduate teaching roles and they conduct both laboratory, i.e. basic research and clinical research related to the neoplastic diseases. With approval of a bone marrow transplant program in Manitoba, additional demands were put on this department to provide optimal total body irradiation treatment. This is an extremely time consuming and complex treatment which already has been successfully given to several patients. Integrated multidisciplinary and site-orientated clinics have continued to expand during the last year to include breast cancer, tumours of the central nervous system, gynecological oncology and lung cancer.

There is a conjoint weekly bone marrow transplantation group meeting in which all the aspects of different components of the management of the patients are being discussed.

Also, a multidisciplinary soft tissue and bone sarcoma conference has become a regular event with a frequency of once a month with the attendance of orthopedic surgeons, general surgeons, medical and radiation oncologists, pathologists and diagnostic radiologists.

Our ultimate goal is that most of out-patient clinics will be conjointly staffed according to the overall integration plan. Recognizing the shortage of nursing , medical and radiation oncology staff, this process will have to develop over a relatively long time.

The weekly head and neck clinic is functioning well with the attendance of clinicians from both Health Sciences Centre and St. Boniface Hospital. The liaison between the Department of Surgery, Internal Medicine, Gynecology and Diagnostic Radiology remains close.

The problem with the shortage of O.R. time for brachytherapy has been resolved, but there is a continuing shortage of brachytherapy beds for non-gynecology patients requiring interstitial radiotherapy. There is an urgent need to upgrade the existing interstitial radiotherapy equipment and serious discussions have been initiated with MHSC concerning the acquisition of a state-of-the-art afterloading machine.

Staffing

Seven Radiation Oncologists are currently on staff with a projected compliment of ten senior staff.

Academic and Scholarly Activities

New Patient Conference every other week.
Integrated Pathology/Radiation Oncology Rounds bi-weekly.
Treatment Planning Meeting weekly.
Research Seminar monthly.
Brain Tumour Conference weekly.
Head and Neck Tumour Conference weekly.
Resident Research Seminars weekly.
Tumour Pathology and Clinical Rounds at St. Boniface Hospital weekly.
Integrated Diagnostic/Therapeutic Radiology Rounds weekly.

Radiotherapy Treatment Floor

The Radiotherapy Treatment Floor located at the M.R. MacCharles Unit has a staff of fourteen registered technologists with the support of two unit assistants and a receptionist. During the fiscal year of 1990/1991 a total of 1,817 patients received radiation therapy, of whom 1,243 were new patients and 574 were being retreated. A total of 21,716 treatments were given, which represents a significant reduction from last year (ie: down from 26,231 treatments) due largely to a reduction in the operational hours of the high energy accelerator in October 1990 to 0700 - 1815 hours. As well, the treatment total was lower because the new dual energy accelerator operating hours were reduced to half days in February 1991 so that final calibration for electrons could be accomplished.

The installation and calibration of the 6MV linear accelerator was completed so the department was able to treat our first patient on this unit in late November 1990. Virtually no staff training on this machine was required (nor to the record and verify system) due to the similarities between it and the previously installed accelerator.

The Bone Marrow Transplantation Program got underway in late 1990.

Clinical training of the radiotherapy students remains a significant part of our departmental activities. We are now fortunate to have three technologists who took the C.P.R. instructors course and they are able to provide the yearly re-certification of the technologists. Along with this, a commitment to ongoing staff education remains a goal of our department.

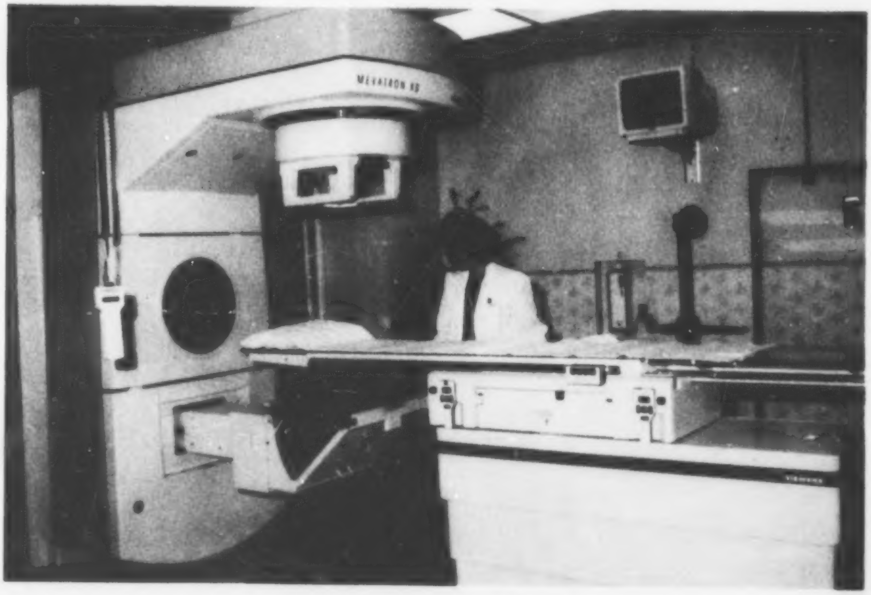
This coming fiscal year we look forward to the continuation of the Bone Marrow Program, which relieves the need for those patients to have to seek treatment outside the province. It is also anticipated that on-line portal imaging will get into full clinical use. As well, it is hoped that the dual energy accelerator will be utilized to its fullest capacity.

Even with the complexity of treatments and the introduction of new techniques, the technologists continue to retain a commitment to compassion in their clinical work.

Clinical Investigations

Portal Imaging Project

This project is being jointly run between the Departments of Radiation Oncology and Medical Physics with support from Siemens. Over the past several years a system has been developed consisting of an imaging camera and associated hardware and software which permit acquisition of portal images during patient therapy. This system is now being integrated into clinical practise as part of a study. The on-line portal images obtained are viewed real-time by the treating clinician and any significant deviations from the intended treatment can be corrected immediately. The images may also be digitally sorted and enhanced in a variety



Research

Basic research involves Immunology whereas clinical research involves development and clinical implementation of on-line portal imaging, CT based treatment planning, experimental protocols involving radiotherapy in different forms of systemic treatments. The department is actively participating in the large co-operative groups such as NCIC, NSABP and RTOG.

of ways and used to objectively assess organ or patient movement between fractions and accuracy of the actual treatment compared to the clinician's plan. Software is under development for the automatic comparison of digital images by computer. The daily portal images can be combined into a movie-loop which can give an objective record of the inter-fraction variability throughout a course of radiation therapy.

It is also intended that the study will investigate the use of immobilisation devices other than the traditional perspex shell, as well as the use of graticules and partial transmission blocks.

Value of Three Dimensional Planning in Radiotherapy Treatment (3-D)

The 3-D planning project is a joint project between the Department of Medical Physics and the Department of Radiation Oncology. The aim of the project is to test the hypothesis that outlining the tumour volume in 3-D, rather than the present convention of using only two dimensions, will be of benefit to the patient. From the clinical point of view, 3-D planning will result in lower dose to nearby normal tissues which hopefully will be reflected in the presumed benefit to the patient of less normal tissue reactions and perhaps the ability to increase the dose to the actual target volume to achieve better local control. Our study is prospective and does not lead to any changes in the patient's conventional treatment. The patient's conventional data are used in parallel with 3-D theoretical planning to test the hypothesis that using 3-D planning will result in lower dose to surrounding normal tissue structures and sparing of certain sensitive organs with accurate treatment of the target area. The project is active at the moment and so far eight patients have been entered.

Laboratory Investigations

THE EFFECT OF ESTRADIOL AND TAMOXIFEN ON LYMOPHOCYTE REACTIONS

Edward Baral and Istvan Berczi, Department of Immunology, University of Manitoba.

We have demonstrated that tamoxifen influences suppressor T-cells by leading to an increase in IgM release by pokeweed mitogen stimulated B-lymphocytes. It was also demonstrated that tamoxifen influences the cytotoxic properties of peripheral blood lymphocytes against autologous tumour cells in vitro. The current studies focus on the investigations of calcium influx and intracellular mobilization as possible mechanisms by which tamoxifen influences lymphocyte proliferation. The experiments are being performed with regard to the identification of the receptor through which tamoxifen influences calcium metabolism. At the present time, the tamoxifen and estradiol's effect on the capacity of peripheral blood lymphocytes to produce interleukin-1, interleukin-2, tumour necrosis factor and interferon gamma are studied. Furthermore, the effect of tamoxifen on LAK cell mediated cytotoxicity and on JL2 and gamma interferon receptor expression on human lumphocytes are being studied. The information obtained from these experiments may not only provide insights for more rational use of tamoxifen, but also open up a novel area of hormonal treatment of immunological disorders.

1990 Statistics

	MacCh	SBGH	Total
Patient visits	19,189	3,577	22,766
Treatments	22,774	5,727	28,501

NUMBER OF TREATMENTS WITH RADIOACTIVE SOURCES

Cesium 137	Gold Grains	Iridium 192 Applicator	Beta	Total
99	0	1	40	140

Publications

Baral, E., Auer, G. In vitro effect of Adriamycin on non-proliferating and proliferating epithelial cells. Int. J. Rad. Onc. Biol. Physics 19:4:963-965, 1990.

El Sayed, S., Symonds, R.P., Robertson, A.G., Paul, J., McGarva, J. Phase II trial of carboplatin and vinblastine in advanced squamous cell carcinoma of the head and neck. Cancer Chemother. Pharmacol. 26:464-466, 1990.

RADIATION THERAPY TECHNOLOGY TRAINING PROGRAM

Elvera Kirk, R.N., A.C.T., C.A.E., *Program Coordinator*
Kathy Suderman, R.T.T., *Deputy Program Coordinator*

1990 saw the first class of students graduate from the revised and restructured training program established in 1988. I am pleased to report that four students graduated from the Manitoba Program, and two from the Saskatchewan Program which is now affiliated with us. All six of these graduates were successful in obtaining registration in the profession via the National Certification process. Congratulations to Karen Ann Johnson, Susan Johnson, Brian Lucyshyn, Christine Sveinson from Manitoba, and Rob Thibault and Joe Andreas from Saskatoon.

Following is the enrolment in the program as of May 1990:

1st Year:	Manitoba	4 students
	Saskatchewan	8 students
2nd Year:	Manitoba	6 students

During this past year, Dr. K. Malaker left the position of Medical Director for the Training Program. I would like to thank him for his dedication to the training of technologists in this province, as well as for his personal support over the years. We welcome Dr. Stephen Larsson to this position knowing that he too supports the program staff and students. In the fall of 1990 the position of Deputy Program Coordinator was increased from a 0.6 to 0.8 E.F.T. in order that Mrs. Kathy Suderman could increase her teaching time in the program. With the resignation of Dr. Dunscombe, Kathy accepted the responsibility for the Physics and Apparatus Course. Our thanks to Dr. Dunscombe who developed this course as well as the study package, and therefore, made it a much easier task for Kathy than it might have been.

Our major purchase this year was a computer to be used by both staff and students in this program.

We continue to enjoy and benefit from the participation of Saskatchewan students in year one of our program in spite of the fact that this increased class size taxes both our physical and human resources. We look forward to the improved physical facilities of the new building.

RECORDS AND REGISTRY

G. Hanson, CCHRA(A), *Interim Director*
H. Whittaker, CCHRA(C), *Director* (effective March 1991)
L. Walesiak, *Secretary*

Central Cancer Registry

J. Kostyra, *Supervisor*
S. Bremner, L. Bonnar, M. Parisien, C. Jonatanson, J. Walker, *Cancer Registry Officers*
R. Bresch, *Death Clearance Clerk*
F. Shilshtut, *Admission/Separation Clerk*
A. Cookson, *Pathology /Cytology Processing Clerk*
C. Hildebrand, R. Zaroda, *Clerical Support*

Health Records Services

E. Tower, *Supervisor*
C. Johnson, *Intake Coordinator*
L. Harder, M. Hammerback, *Records Processing Clerks*
L. Arsenuik, M. Humphreys, *File Control Clerks*
C. Beder, D. Charney, K. Goertzen, M. Halischuk, D. Meakin, V. Tuckett, *Medical Transcriptionists*
K. Whalen, *Interview Clerk*
M. Varkerti, *Courier/Mail Services*
G. Haufschild, *Receptionist*

St. Boniface Unit

G. Noonan, *Supervisor*
K. Isaak/D. Penner, *Cancer Registry Officers*
J. Olson, G.Taylor, L. Soshycki, *Medical Transcriptionists*
K. Friesen, *Records Processing Clerk*
M. Morrison, *File Control Clerk*
C. MacLean, *Receptionist*

The Records and Registry Department is the health information processing center for the Manitoba Cancer Treatment and Research Foundation. A fully integrated, computerized environment, its organizational configuration and activities through 1990 were as follows:

Health Records Services

This unit's scope of service comprises the following:

Health record filing, control and retrieval
- Provision of approximately 83,000 health records for clinical purposes.

Medical transcription
- Transcription of 692,000 lines of dictation

Patient registration
- Initial interview and registration of 2,861 new patients

Intake co-ordination
- Management of 2,329 consultation requests for radiotherapy treatment

Records Processing
- Maintenance of health records, including placement of approximately 100,000 reports
- Medicolegal correspondence

Reception and switchboard services
Courier services/mail processing

The department continued throughout the year to modify and enhance systems and procedures to provide efficacious health record services.

During 1990, the Forms Committee implemented/revised a number of health record and nursing data forms. Departmental participation in the Co-ordinating Committee continues as well on an ad hoc basis for health record control issues presented by clinical staff.

A project was undertaken to collect, code and disease index all current and archived slides for teaching purposes.

Central Cancer Registry

The Foundation has been legally mandated since 1937 to collect, register and maintain data on all cancer cases for the Province of Manitoba, with a view to providing:

a) an accurate cancer incidence data base for health care planning and quality assurance.

b) a research data base for detailed study of malignant disease (including epidemiological studies and health care delivery analyses).

Data sources include: Cytology and Pathology Departments, the Department of Vital Statistics, the Manitoba Health Services Commission's Hospital Abstracting System, individual physicians' offices and clinics.

The Foundation's Epidemiology and Biostatistics Department remains the largest single user of Registry data. The remainder of users consists of the health and research communities, government, business and the public, which are increasingly interested in cancer incidence rates as they relate to causative factors and prevention. The integration of Registry and treatment record data within this population-based Registry provides approved researchers with a valuable comprehensive database.

The Registry continues to contribute yearly data to the National Cancer Incidence Reporting System at Statistics Canada, through which data is forwarded to the International Association of Cancer Registries, which publishes world cancer statistics. Efforts continue through the National Cancer Registries Association towards development of a population-based Canadian Cancer Registry.

In 1990 two representatives from the Registry attended a National Registries Technical Workshop, sponsored by the National Cancer Registries Association, and hosted by Statistics Canada in Ottawa. Data comparibility and quality assurance were discussed with a view to promoting standardization across Canada.

Requests for information processed through the Registry in 1990 included:

1) Provision of disease-related data for diagnostic clarification and treatment planning	1,106
2) Basic statistical requests (published incidence and/or mortality rates, etc.)	8
3) Studies and Research Projects:	
a) Statistical requests requiring custom tabulation and/or case ascertainment	35
b) Studies requiring technical assistance	17
c) Studies on-going from previous years	14
d) Internal Quality Assurance reviews	9
TOTAL	**1,189**

St. Boniface Unit

Our satellite Health Records and Registry Unit continues to provide corresponding services to our St. Boniface Oncology Department. The unit experienced an increase in demand for services as the St. Boniface Unit takes on a greater patient load.

With the anticipated installation of new radiotherapy treatment units, the Records and Registry Department will relocate. The new Records Department will provide more efficient working and records storage space.

Representation on the Manitoba Cancer Treatment and Research Foundation Forms Committee assured that St. Boniface Oncology health records forms remained consistent with those utilized at the MacCharles Unit.

SOCIAL WORK

Betty Wong, M.S.W., R.S.W., *Director*
Len Perry, B.S.W., R.S.W., *Social Worker*
Anneliese Friedle, *Secretary*

The mandate of Oncology Social Work is to assist patients and their families to make optimum use of medical and psychosocial services in order to achieve their fullest possible physical, emotional, spiritual and social well-being. Social Work recognizes the tremendous impact illness has on the complete family unit. We therefore endeavour to provide services to patients, their families and/or significant others to prevent unnecessary stress and disintegration. These services are provided in consultation with medical staff and other professionals.

Referrals come from patients/families themselves, physicians, nurses, other professionals within the hospital complex, and our colleagues in the community.

Counselling services continue to demand a greater percentage of our time. Patients and families often require supportive and adjustment therapy to cope with the emotionally charged issues related to all the aspects of diagnosis, medical treatment and follow-up care.

Practical needs such as financial assistance, housing and transportation are addressed through resource counselling. Many referrals are made to other departments within the medical complex as well as agencies within the community.

Interdisciplinary conferences are used to share information, formulate treatment plans, discharge plans and follow-up care. In a majority of cases the social worker continues to be the prime therapist and/or case manager. This method minimizes the confusion and frustration patients and families sense when dealing with a multitude of care providers.

Our department coordinates the fall session of the Kids Can Cope program, an educational support group for children 5 - 18 years, who have a family member or close significant other with cancer. Department members are also active in associations and organizations that seek to assess and enhance the skills and programs we use in meeting the psychosocial needs of our patients and families. Our aim is to keep updated on current methods and programs to provide our clients with the best available care.

We continue to provide field placement for social work students from the University of Manitoba. In addition, our department is involved in the clinical training for students of other disciplines.

The Social Work Department continues to function as an integral part of the health care team helping to meet the challenging and increasing demands of our patient population.

SURGICAL ONCOLOGY

Wayne Beecroft, D.D.S., M.D., FRCPC, FACS, *Director*
Barry Anderson, M.D., FRCSC

Residents

M. Al-Naami, M.D.
D. Clark, M.D.
L. Garber, M.D.
J. Meisner, M.D.
R. Biewald, M.D.
Z. Downar-Zapolski, M.D.
P. Gray, M.D.
J. Robinson, M.D.

Organization

The Section of Surgical Oncology provides consultation and treatment in ambulatory clinics conducted daily in the facilities of the Manitoba Cancer Treatment and Research Foundation. New patient referrals are given priority and every effort is made to expedite diagnosis and staging for individuals suspected of having cancer. The availability of a dedicated minor procedures room facilitates endoscopy and biopsies. The service enjoys ready access to sophisticated diagnostic services at the Health Sciences Centre. The goal of the service is to provide prompt identification of patients with cancer, efficient determination of extent of disease and appropriate treatment planning.

At present, multimodality care is the norm for managing malignant disease. The on-site availability of consultants from Medical Oncology and Radiation Oncology reduces delays in obtaining expert advice and planning the sequence and components of combined modality therapy. The concept of integrated clinics extends to the inpatient facilities at the Health Sciences Centre. A designated hospital ward provides care for both Surgical and Radiation Oncology patients and affords an opportunity to continue the joint management initiated in ambulatory clinics.

Although surgical consultation is available for patients with all forms of malignancy, the service activity is dominated by certain tumour types: head and neck cancer, breast cancer, melanoma and sarcoma.

Teaching

The Surgical Oncology Service is a component of the Section of General Surgery of the Department of Surgery of the University of Manitoba. Housestaff are assigned to the Service and include senior medical students, interns, and residents from both the Department of Surgery and Otolaryngology. These trainees enjoy an opportunity to participate in the care of patients with cancer including initial assessment, inpatient care, operations and subsequent follow-up. When compared to the experience available on other surgical units, Surgical Oncology is an unusual example of the purposeful integration of all aspects of patient care. Several allied disciplines rotate residents to the Surgical Oncology Service, including Oral Surgery, Radiation Oncology and Medical Oncology. There are several teaching sessions scheduled throughout the week. Housestaff participate in the Conjoint Clinic for Head and Neck Tumours, a weekly pathology round, a combined surgery-radiotherapy ward round and a weekly conjoint audit round to critically review concurrent patient care. In addition, the Service participates in the complete roster of educational rounds scheduled through the Department of Surgery.

Clinical Investigation

The Service is committed to continued support of NSABP and NCIC protocols. Several initiatives are being developed to exploit the clinical experience gained in caring for cancer victims. The large volume and variety of head and neck cancer treated by the service is being evaluated for suitable protocol design and implementation. Current treatment approaches are monitored and constantly revised in reference to published experience and local results.

STATISTICS FOR 1990

New Patient Referrals	676
Follow-up Visits	2,274
Total Patient Visits	2,950
Outpatient Procedures:	
Endoscopy	58
Biopsies	240
Other Procedures	12

Head and Neck Tumor Conference and Clinic

Dr. W. Beecroft and Dr. S. Larsson
(Joint Co-ordinators)

The Conjoint Clinic for Head and Neck Tumours was established in 1971 and has continued to provide a weekly forum for patient assessment and management review. Interested consultants, housestaff, nurses and various trainees attend the conference and subsequent combined discipline clinic. Patients are examined, physical findings documented, diagnostic studies reviewed and treatment options thoroughly discussed. The goal of the conference is to provide a consensus, whenever possible, as to the best treatment plan given each patient's condition. The conference provides an efficient forum to discuss several cases in detail and to illustrate the basis of clinical decision making to trainees. The complex patient factors and extensive treatment options which form the basis of therapy are best developed in relation to a particular patient's circumstance.

The continued support of Dr. Alguacil, Pathology, Dr. Sutherland, Radiology and Dr. Odlum, Dentistry, is greatly appreciated.

The Conjoint Clinic has proven to be one of the most successful disease-site clinics and the participants, both patients and staff, are well served by the weekly exchange of ideas and management review.

VOLUNTEER SERVICES

Elaine Hickerson, *Coordinator*

During 1990/91, 186 volunteers provided 14582.75 hours of volunteer service. Orientation and training was provided for 52 new volunteers. Refreshments, provided by the Canadian Cancer Society, were served to 58,305 patients and family members. On April 25th, 1990, Bonny Kahanovitch accepted the Mayor's Volunteer Service award for Health on behalf of our volunteers. All volunteers who had given 750 hours of service attended the luncheon at which the award was presented. 22 M.C.F. volunteers were part of this gala gathering.

Mr. Barry Adams, of the Board, and Great West Life hosted a wine and cheese reception for our volunteers on June 7th. Pins were presented to all volunteers who had given 500 hours of service. Names of those who had given 1,000 hours of service were placed on a plaque. Volunteers Ella Adams, Rosella Genik, Tony Gregorash, Bonny Kahanovitch, Kay LeFevre, Rose Marier, Lorna Marshall, Shirley Poole and Dorothy Rankin were recognized in this way. Shirley Poole and Lillian Danish were presented with the Bonny Kahanovitch awards for outstanding service.

Three volunteers, Rosella Genik, Tony Gregorash and Kay LeFevre had given over 2,000 hours of volunteer service to March 31, 1991.

Volunteers held a raffle and bake sale for the building fund. $469.15 was raised. Volunteers sold daffodils for the Canadian Cancer Society and also delivered daffodils which had been purchased by business to cancer patients in all areas of the Health Sciences complex. We have continued to respond to requests for volunteers for the Nurses Education Fund Sales.

The Newsletter was published four times during the year. We were fortunate to recruit Bert Surtees, who has desk top publishing skills. The work of our volunteers was featured in the Manitoba Society of Seniors newspaper.

The coordinator participated in the University of Winnipeg Recruitment Days sponsored by the Volunteer Centre. Hugh John McDonald School Career Days provided another opportunity to recruit students. The coordinator was invited to Joseph Wolinsky Collegiate to present certificates to students who had volunteered at the Cancer Foundation.

Three volunteers and the coordinator attended the Manitoba Hospice Conference "Quality Living in a Limited Time". Three volunteers took the visitor training program offered by the Manitoba Hospice Foundation.

Four volunteers and the coordinator attended sessions of the MHO conference which featured a session on the volunteer/client relationship.

Our work experience program has expanded to include a research project for the department of nursing. A human ecology student is documenting the nutritional requirements of cancer patients.

Cansurmount volunteers who have had bone marrow transplants are now visiting in the clinics as well as on D6.

Christmas hampers were provided for 30 families. Staff and volunteers worked very closely on this project. CUPE Local 1550 and the Manitoba Association of Health Care Professionals as well as individual donors gave $1,363. Expenses were $1010. $100 in emergency aid was given since the hamper project was completed.

The Coordinators Resource Committee - Barbara Warren, Director of Nursing, Nancy Johnson, Senior Chemotherapy Nurse, Betty Wong, Oncology Social Work, representing the Cancer Foundation and Sue Borrett, Patient Services Administrator, Elaine Enns, Chairman of the Patient Services Committee and Hazel Quinton, representing the Canadian Cancer Society, Manitoba Division, continue to support the volunteer program. Meetings have been held to discuss the role statement and the Volunteer Services requirements for the Functional Program.

Throughout the year, volunteers have provided additional services and comforts for patients and family members, supplemented the work of staff by performing non-professional duties, and enhanced public relations within the Cancer Foundation and throughout the community.

VOLUNTEERS 1990- 1991

George Ackerman
Ella Adams
Livvy Aftanas
Kay Ahoff
Monica Allison
Patricia Amaral
Susan Armstrong
Evelyn Badger
Dorothy Barker
Angela Barratt
Rejane Bernier
Wanda Berezanski
Ina Berthelette
Aimee Bilotto
Audrey Bird
Thelma Bird
Clara Black
Helen Boese
Margaret Bonar
Margaret Booth
Lannie Bosman
Mary Bosman
Cheryl Bowman
Michelle Bresch
Beulah Brick
Marjorie Brotheridge
Cy Bruder
Martin Brudy
Linda Buechler
Rita Burdeiny
Steve Burdeiny
Mary Carey
June Carter
Tammy Chesley
Twan Chu
Ethel Coakes
Shirley Cohen
Edna Convey
Grace Corder
Fran Crowston
Helen Craig
Marj Currie
Anita Cule
Lillian Danish
Shubha Das
Marci Davis
Barbara Deacon
Sophie Didych
Michelle Du
Melanie Dyck
Nell Dyck
Tara Elder
Betty Ellis
Jennifer English
Linda Finkleman
Luba Finney
Lisa Forbes
Louise Garbutt
Sylvia Gaska
Rosella Genik
Cecile George
Verna Gibson
Esther Ginpil
Tony Gregorash
Nancy Halas
Norma Haslam
Pat Hetherington
Lillian Hill
Doreen Hlady
Linda Holloway
Michelle Horkoff
Susan Hosein
Mary Inkster
Julie Isleifson
Ina Jablonski
Lorraine Jenkins
Norma Jones
Bonny Kahanovitch
Dalit Kahanovitch
Yael Kahanovitch
Audrey Keber
Susan Keller
Linda Kerr
Frieda Klippenstein
Emma Lamb
Kay LeFevre
Doreen Laxdal
Jill Leggett

Joan Lovel
Margaret MacLeod
Mary MacPhee
Peggy Mahon
Doris Mahoney
Marla Mainer
Liz MacCuish
Anne Mackay
Nanette Magill
Rose Manchulenko
Kayla Mandshein
Rose Marier
Lorna Marshall
Bev Mathieson
Esther McCubbin
Angela McDonald
Jill McDonald
Pearl McDowell
Dorothy McEachran
Alice McIntosh
Kathleen McKay
Mary Louise McKenzie
Violet McKenzie
Alice McLennan
Lynda McNeill
Connie Meunier
Jeanette Milliken
Dora Moir
Emily Murphy
Phyllis Nazeravich
Anne Neal
Marion Newsham
Netta Nicholson
Monelle Oman
Rowena O'Quendo
Marcia Palavacino
Berthe Palud
Louis Palud
Paul Palud
Bernice Peichl
Jocelyn Pelayo
Adair Phelps
Marlene Pestrak
Shirley Poole
Angie Popowich
Barbara Prosser
Janet Purdy
Doris Quinn
Andrew Rankin
Dorothy Rankin
Del Ritchie
Danielle Rivalin
Marianne Robertson
Kay Rokola
Eva Rondeau
Sarah Runions
Sheila Sampson
Mabel Sayer
Sharon Schaffer
Helen Scoble
Bev Scott
Robert Schaepe
Lorraine Shields
Sheryl Singer
Margaret Slater
Dorothy Sly
Vera Smeaton
Christine Sorko
Phyllis Sowerby
Erin Stein
Jean Stewart
Bert Surtees
Terry Sveinson
Margaret Swayze
Walter Swayze
Tamara Szajewski
Lorraine Tennant
Blanche Thomson
Ressa Tod
Betty Todd
Wilma Tolentino
Kerry Tomy
Daisy Tooth
Devon Ungurain
Helen Vidal
Mae Vince
Merl Voakes
Terese Vodon
Olive Wagner
Shirley Wallbridge
Lynne Waller
Trudy Waller
Sandra Webb
Joan Wazny
Kristen Whalen
Brent Wilde
Mary Wolfe
Terry Wood

VOLUNTEER SERVICES - CANADIAN CANCER SOCIETY

Helen Morrow, *Patient Assistance Advisor*
Monica Dinney, *Patient Assistance Advisor*

The Patient Services programs of the Canadian Cancer Society provide practical assistance and emotional support to both cancer patients and their families in Manitoba.

In the fall of 1990 the Society released findings from its comprehensive study of "The Needs of Cancer Patients Living in Manitoba." The findings point to a number of unmet needs within the province and have far-reaching implications for provision of support services to cancer patients by the Manitoba Division, as well as for other health organizations and facilities providing diagnostic and treatment care.

Using the results of this report, the Society will actively examine ways of improving existing services as well as new programs to assist those affected by cancer.

To help cancer patients and their families deal with the complications arising from bone marrow transplants, a group of patients and family members formed a Bone Marrow Transplant Support Group in the summer of 1988. In October 1990 the group affiliated with the Canadian Cancer Society which now provides the group with emotional support training and financial support.

"Kids Can Cope," a joint program of the Society, The Manitoba Cancer Treatment and Research Foundation and the St. Boniface General Hospital, continued to offer support to children who have a parent, sibling, relative or friend with cancer. It helps children and teenagers to learn about cancer and its treatment and to share feelings and concerns in a supportive environment. Two programs were conducted in the spring and fall.

The Society continued its involvement in summer camps for children and young adults touched by cancer. Four camps were held in 1990 including a children's camp, two teen and young adult camps and a family camp. The camps provide a relaxed setting for children and their families to spend time together outside of a hospital setting.

All funding for the camps is provided by the Society. The children's camp is organized by the Children's Pediatric Oncology Clinic, the teen and young adult camps by the Children's Hospital oncology social worker and the family camp by Jeffrey's Folks, a Canadian Cancer Society emotional support group.

Other services of the Society continued to serve a wide range of needs for Manitobans of all ages:

For rural Manitobans travelling to Winnipeg for treatment, convenient economical accommodation was available at Lennox Bell Lodge adjoining the Manitoba Cancer Treatment and Research Foundation. The Society provides 50 per cent subsidization of room rates for a cancer-related stay. Advance bookings are recommended.

Cancer patients used the Volunteer Driver Program to get to and from treatment, with approximately 50 rides per day being provided in 1990. Also in 1990, the Masons in rural Manitoba mobilized to bring patients to Winnipeg and to rural treatment centres. The Society subsidizes this program, keeping patient costs to a minimum.

Trained CanSurmount visitors provided emotional support to many newly diagnosed cancer patients. Having experienced cancer themselves, these visitors are in a unique position to offer emotional support. CanSurmount Volunteers are available to visit either in the home or in the hospital and also visit informally in three treatment areas of the clinic: chemotherapy, radiotherapy and the head and neck clinic.

Volunteers with the Society's Reach to Recovery program helped mastectomy patients come to terms with their surgery. Having experienced breast cancer personally, these visitors are sensitive to the necessary adjustments in body, mind and spirit, giving emotional support and practical advice.

Time spent in the treatment clinic waiting room was made easier for many patients and family members by the efforts of the Refreshment Service Volunteers who provided hospitality and over 60,000 snacks to Manitobans in 1990.

The New Voice Club continued to provide emotional support and practical advice to people needing a laryngectomy or having just undergone the surgical procedure.

Throughout 1990, Jeffrey's Folks continued to provide emotional support, information and friendship to the parents of children with cancer.

Adults and children undergoing cancer treatment had ready access to over 500 refurbished wigs as well as turbans and scarves through the Society's Wig Service. All are available at no charge.

The Society's Financial Assistance Program, established with the philosophy that no patient miss treatment because of financial hardship, continued to cover the cost of accommodation and transportation for needy rural patients.

People living with cancer look for comfort, meaning, dignity and hope in their personal struggle with the disease. The Patient Services programs and dedicated Volunteers of the Canadian Cancer Society, Manitoba Division, are there to assist.

MANITOBA INSTITUTE OF CELL BIOLOGY

MANITOBA INSTITUTE OF CELL BIOLOGY

A. H. Greenberg, M.D., Ph.D., *Director*
J. A. Wright, Ph.D., *Associate Director*
N. Ryan, *Administrative Assistant*

Senior Members

Asher Begleiter, Ph.D.
Donna Chow, Ph.D. (until Nov. 1990)
Gerald J. Goldenberg, M.D., Ph.D. (until Aug. 1990)
Arnold H. Greenberg, M.D., Ph.D.
James Johnston, M.D.
Michael Mowat, Ph.D.
Brent A. Schacter, Ph.D.
Jim A. Wright, Ph.D.
Lorne J. Brandes, M.D.
Jon M. Gerrard, M.D., Ph.D.
Sara J. Israels, M.D.
H.Y. Peter Lam, Ph.D.
Frixos Paraskevas, M.D.
Eva Turley, Ph.D. (from July 1990)

Associate Members

Janice Dodd, Ph.D.
Nasreen Khalil, M.D.
E.D. Israels, M.D.

Research Associates and Post Doctoral Fellows

Frances Amara, Ph.D.
Abdulai Deffie, Ph.D.
Aiping Huang, Ph.D.
Nidhi Jain, Ph.D.
Masahiro Nishibori, M.D.
Satya Saxena, Ph.D.
Lianfi Shi, Ph.D.
Euan Taylor, Ph.D.
Pardeep Bhatia, Ph.D.
Julia Green-Johnson, Ph.D.
Robert Hurta, Ph.D.
Archie McNicol, Ph.D.
Shanti Samuel, Ph.D.
Lois Schwarz, Ph.D.
Maureen Spearman, Ph.D.
Steve Zalcman, Ph.D.

Graduate Students

Mohamed Abdelhaleem, M.D.
Raquel Baert, B.Sc.
Yongzhong Chen, B.Sc.
Bob Choy, B.Sc.
Jacqueline Damen, B.Sc.
Jason Falk, B.Sc.
Geoffrey Hicks, B.Sc.
Lorne Janz, B.A.
Eugene Roussel, M.Sc.
Gerald Stelmack, B.Sc.
William Taylor, B.Sc.
Catherine Vriend, B.Sc.
Wenzheng Yang, B.Sc.
Asim Ashique, B.Sc.
Susan Battistuzzi, B.Sc.
Christine Chiu, B.Sc.
Genevieve Curpen, B.Sc.
Feng Deng, M.Sc.
Christine Hall, M.Sc.
Stephen Hrushovetz, B.Sc.
Ricky Kraut, M.Sc.
Paul Sandstrom, B.Sc.
Esther Taylor, B.Sc.
David Tough, B.Sc.
Ping Yang, M.Sc.
Zuo Li, M.D.

Summer Students

Mitch Bruneau
Michele Lajzerowicz
Arthur Pang
Paul Syslak
Mark Janzen
Gavin MacBeath
Anne Robbins
Shirley Tse

Technicians

Carol Berard
Pat Bogdanovic
Anna Chan
Valerie Cripps
Elena Duta
Nina Hunt
Michael Jesson
Kristine Lee (nee Tang)
Eileen McMillan
Robert Myers
Anne Robbins (part-time)
Pauline Robinson
Mary Sauder
Mukhtiar Singh
Balram Sukhu
Michael Talgoy
Linda Verburg
Oliver Bereznay
Dan Bosman
Arthur Chan
Lynn Desilets
Pauline Gerrard
Shelly James
Angela Kemp
Marsha Leith
Paul Moreira
Sandra Oh
Catherine Robertson
Erica Robotham
Rupinder Singal
Sandra Singhroy
Anand Sukhan
Jiangang Tong

Lab Assistants

Irene Freiter
Maria Monch
Adi Limpach
Inga Tober

Secretaries

Nikki Ryan
Sonia Tsutsumi
Susan Snusher
Agnes Warkentin

Visiting Scientists

Dr. Svetlana Dolina, Ben Gurion University, Israel
Dr. Lev Hatzkellson, Ben Gurion University, Israel
Dr. Abe Shalev, Rishoen Le Zion, Israel

The Manitoba Institute of Cell Biology was founded jointly by the University of Manitoba and the Manitoba Cancer Treatment and Research Foundation in 1969. The purpose of the Institute is to carry out research and training in cancer and other diseases by studying disease mechanisms at a cellular and molecular level. The Institute of Cell Biology is governed by an independent Board of Management consisting of eleven members, three appointed by the University of Manitoba, three appointed by the Manitoba Cancer Treatment and Research Foundation and five jointly appointed by both sponsoring Institutions. The Manitoba Institute of Cell Biology is housed in the Manitoba Cancer Treatment and Research Foundation, adjacent to the Faculty of Medicine, University of Manitoba and the Health Sciences Center.

The Institute of Cell Biology consists of a Director, twelve senior investigators, and ninety-five staff including research associates, postdoctoral fellows, graduate students, technicians, laboratory assistants and secretaries. Although the Institute of Cell Biology is not a degree-granting body, advanced degrees at the Masters or Ph.D. level may be obtained with any of the departments in the Faculty of Medicine, University of Manitoba. The major emphasis of the research program of the Institute of Cell Biology has centered on the fields of Molecular Biology of Tumor Progression, Biochemical Pharmacology of Drug Resistance, Immunology and Hematology. Senior investigators hold cross-appointments in many University departments including the Departments of Immunology, Genetics, Biochemistry, Physiology, Microbiology, Medicine and Pediatrics.

The location of the Manitoba Institute of Cell Biology in the Manitoba Cancer Treatment and Research Foundation building has enabled the development of parallel programs of basic and clinical investigation of patients with neoplastic disease. Patients with a wide range of neoplastic disorders are available for investigation conducted by senior investigators in the Institute. Not only is this interaction facilitated by a geographical juxtaposition of the two Institutions, but also by the fact that many senior investigators hold cross-appointments in the Manitoba Institute of Cell Biology and Manitoba Cancer Treatment and Research Foundation.

Major programs in the Manitoba Institute of Cell Biology have been continually supported by the NCI since the founding of the Institute group in 1969. During 1990, members of the Institute raised $3.24 million dollars in research funds, of which $0.5 million was for career awards, postdoctoral fellowships and studentships. Funding sources include the NCIC, MRC, NSERC, NIH, many smaller foundations, as well as private industry (Bristol-Myers, Park Davis, RJ Reynolds). This represents one of the highest per capita funding rates of all the University Departments.

Report of the Director

In the last year, the Institute saw many changes in senior personnel, reflecting our overall goal of renewing and expanding our research base. Dr. Eva Turley joined the research program in September, 1990, bringing with her a well developed program on the molecular mechanisms of cell locomotion. Dr. Turley now has her laboratory operational and has moved quickly to establish productive collaborations with other members of the Institute.

Dr. Nasreen Khalil was recently appointed an Associate Member of the Institute, and will be establishing her laboratory with the support of the Respiratory Section of the Department of Medicine. Dr. Khalil has been internationally recognized for her exciting research in pulmonary fibrosis, and particularly the role of TGF-β in the early inflammatory reactions of this disease following lung injury with the chemotherapeutic drug, bleomycin. We look forward to her continued success.

The Institute has also completed negotiations with Dr. David Litchfield of the Howard Hughes Medical Institute, Seattle, Washington, and he will be joining us in September, 1991. Dr. Litchfield is a graduate of the University of Western Ontario, and has completed his postdoctoral training with Dr.

Dr. Arnold H. Greenberg

Edwin Krebs on the study of the serine/threonine kinase, casein kinase II. Dr. Litchfield's excellence in protein chemistry and molecular biology, and his many common interests with other members of the Institute in signal transduction pathways, will be a great asset to our group. Dr. Litchfield will also be responsible for the operation of the proposed Protein Biotechnology Laboratory.

We also extend our best wishes to members of the Institute who have moved elsewhere during the 1990 year. Dr. Donna Chow has moved her laboratory to the Department of Immunology at the University of Manitoba. Dr. Gerald Goldenberg has taken a position as the Head of the Oncology Teaching Program at the University of Toronto, while Dr. Peter Lam is returning to Hong Kong where he will be an Associate Professor in a new department. We have enjoyed many years of interaction with these excellent scientists, and wish them well in their new positions.

Awards, Honours and Invited Lectures

ASHER BEGLEITER, Ph.D.

was appointed a MEMBER of the Cancer Grants Panel of the *Medical Research Council of Canada*.

was appointed a MEMBER of the Grants Panel for the *George H. Sellers Endowment Fund for Cancer Research*.

was an INVITED SPEAKER in the *Faculty of Pharmacy, University of Toronto*.

LORNE J. BRANDES, Ph.D.

was a PLENARY SPEAKER at the *International Symposium on Histamine, "New* Perspectives in Histamine Research", Amsterdam, Netherlands.

JON M. GERRARD, M.D., Ph.D.

holds a RESEARCH PROFESSORSHIP from the *Children's Hospital of Winnipeg Research Foundation*.

was appointed a MEMBER of the *Manitoba Heart Foundation Research Advisory Committee*.

was a SYMPOSIUM SPEAKER at the *Circumpolar Health Conference*, Whitehorse, Yukon.

ARNOLD H. GREENBERG, M.D., Ph.D.

was a SYMPOSIUM SPEAKER at the *CIBA Foundation* on the Clinical Applications of TGF-β, London, England

was a SYMPOSIUM SPEAKER at the *15th International Cancer Congress*, Hamburg, West Germany.

was a SYMPOSIUM SPEAKER at the *2nd International Symposium on Psychoneuroimmunology*, Rochester, NY.

was invited to be the KEYNOTE SPEAKER for the *Australian Behavioral Immunology Group*, New castle, Australia.

was a SANDOZ LECTURER, *Walter and Elisa Hall Institute for Medical Research*, Melbourne, Australia.

holds a TERRY FOX CANCER RESEARCH SCIENTIST AWARD of the *National Cancer Institute of Canada.*

NASREEN KHALIL, M.D.

received a RESEARCH SCHOLARSHIP from the *Parker B. Francis Foundation* .

was an INVITED SPEAKER at the *American Thoracic Society: 1990 World Conference* on Lung Health in Boston, Massachusetts.

was an INVITED SPEAKER at the *Aspen Lung Conference 33rd Annual meeting* on Mechanisms of Lung Repair in Aspen, Colorado.

MICHEAL MOWAT, Ph.D.

was appointed the SCIENTIFIC OFFICER, Panel H, *National Cancer Institute of Canada.*

SARA J. ISRAELS, M.D.

was awarded a CERTIFICATE OF APPRECIATION from the *Association for the Care of Children's Health.*

BRENT A. SCHACTER, M.D.

was an INVITED LECTURER at the Department of Pharmacology, *Queen's University,* Kingston, Ontario.

EVA A. TURLEY, Ph.D.

was awarded a RESEARCH SCHOLARSHIP from the *Children's Hospital of Winnipeg Research Foundation.*

was appointed a MEMBER of *NIH Site Visit* to Mammary Tumor Group at Stanford University, San Francisco, California.

was appointed a MEMBER of *NIH Site Visit* to the Curlytail Mouse Facility, Harvard University, Boston, MA.

was a SYMPOSIUM SPEAKER at the *American Society for Complex Carbohydrates,* Ann Arbor, Michigan.

was a SYMPOSIUM SPEAKER at the *International Conference on Differentiation of Normal and Neoplastic Cells,* U.B.C., Vancouver, BC.

was a SYMPOSIUM SPEAKER at the *4th Gordon Conference on Proteoglycans,* Andover, N.H.

was an INVITED LECTURER at the *Hospital for Sick Children,* Toronto, Ontario.

was and INVITED LECTURER at the *Department of Biochemistry, University of Alabama,* Birmingham, Alabama.

was an INVITED LECTURER at the *Department of Biology, University of Pennsylvania,* Philadelphia, PA.

JIM A. WRIGHT, Ph.D.

was a GUEST LECTURER at the *Merrel Dow Research Institute,* Indianapolis, Indiana.

holds a TERRY FOX SENIOR CANCER RESEARCH SCIENTIST AWARD of the *National Cancer Institute of Canada.*

was appointed to the FELLOWSHIP AND SCHOLARSHIP REVIEW COMMITTEE for the *Manitoba Health Research Council of Canada*

was appointed to the MEDICAL RESEARCH SCIENTIFIC REVIEW COMMITTEE for the *Alberta Heritage Foundation.*

was appointed to the SCIENTIFIC REVIEW COMMITTEE for the *George H. Sellers Foundation.*

was appointed a MEMBER of the CANCER GRANTS PANEL of the *Medical Research Council of Canada.*

Post-Doctoral and Student Awards

MOHAMMED ABDELHALEEM, M.D. was awarded a STEVE FONYO STUDENTSHIP of the *National Cancer Institute of Canada.*

JACQUELINE DAMEN, B.Sc. received a *University of Manitoba* GRADUATE FELLOWSHIP.

LEV HATSKELZON, M.D. received a *University of Manitoba Faculty Fund and Children's Hospital of Winnipeg Research Foundation* SCIENTIST AWARD.

GEOFF HICKS, B.Sc. received a *University of Manitoba* GRADUATE STUDENT FELLOWSHIP.

ROBERT HURTA, Ph.D. was awarded a *University of Manitoba Faculty Fund* FELLOWSHIP.

NIDHI JAIN, Ph.D. received a *University of Manitoba Faculty Fund* FELLOWSHIP.

ARCHIBALD McNICOL, Ph.D. was awarded a *Children's Hospital of Winnipeg Research Foundation* FELLOWSHIP.

PAUL SANDSTROM, B.Sc. received a *University of Manitoba* GRADUATE STUDENT FELLOWSHIP.

SATYA SAXENA, Ph.D. was awarded a *Manitoba Health Research Council* FELLOWSHIP.

LOIS SCHWARZ, Ph.D. received a *Manitoba Health Research Council* FELLOWSHIP.

ABRAHAM SHALEV, Ph.D. received a *Children's Hospital of Winnipeg Research Foundation* VISITING SCIENTIST AWARD.

MAUREEN SPEARMAN, Ph.D. was awarded a *Medical Research Council of Canada* FELLOWSHIP.

WILLIAM TAYLOR, B.Sc.received a *National Science and Engineering Research Council* STUDENTSHIP.

DAVID TOUGH, B.Sc.received a *University of Manitoba* GRADUATE STUDENT FELLOWSHIP.

Visiting Seminar Speakers

Mario Estable, *Applied Biosystems Canada Inc., Mississauga, Ontario* New Methods of Automated Electrophoresis for Protein, Peptide & Nucleic Acid Purification & Analysis Including Capillary Electrophoresis and Electrophoretic Chromatography

E. Kardami, Ph.D., *Department of Physiology, St. Boniface Hospital* Basic Fibroblast Growth Factor (bFGF) in the Heart, in Health and Disease

Richard Nash, M.D., Ph.D., *Fred Hutchinson, Seattle, Washington* Hematopoietic Growth Factors: Development of a Preclinical Model

Jan Dodd, Ph.D., *Department of Physiology, University of Manitoba* Genetic Changes in Prostatic Neoplasias

Leigh Murphy, Ph.D., *Department of Biochemistry, University of Manitoba* Mechanisms Associated with Resistance to Anti-Estrogens and Progestins in Human Breast Cancer

Robert Shiu, Ph.D., *Department of Physiology, University of Manitoba* Estrogen Regulation of c-*myc* Expression in Breast Cancer

Steven Elledge, Ph.D., *Baylor University, Houston, Texas* Regulation of Ribonucleotide Reductase in Yeast

John Schrader, *Biomedical Research Centre, University of British Columbia, Vancouver, British Columbia* Regulatory Factors in Hematopoiesis: Cytokines and Hematopoiesis

Paul Jolicoeur, *Laboratory of Molecular Biology, Clinical Research Institute of Montreal, Montreal, Quebec* Cell Transformation and Immunodeficiency Induced by Murine Retroviruses

Chris Bleackley, *University of Alberta, Edmonton, Alberta* Attack of the Killer T Cells

Hans U. Lutz, M.D., Ph.D., *Swiss Federal Institute of Technology Zurich, Switzerland* The Role of Naturally Occurring Antibodies and of Complement in Clearance and Phagocytosis of Human Red Blood Cells

Ranjana Bird, Ph.D., *Department of Foods and Nutrition, University of Manitoba* Diet and Colon Cancer Prevention: Role of Animal Models

Francine Rendu, *Hopital Lariboisiere, Paris, France* Signal Transduction and Tyrosine Kinase Activity in Human Platelet Activation

David Litchfield, *Howard Hughes Medical Institute, Seattle, Washington* Protein Phosphorylation in Signal Transduction Events: The Role of Casein Kinase II

Patricia Steeg, *Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Maryland* A Novel Gene, nm23, Homologous to Nucleoside Diphosphate Kinase is Associated with Low Metastatic Potential

Frans A. van der Hoorn, *Department of Medical Biochemistry, University of Calgary, Calgary, Alberta* Testis-Specific Gene Regulation of c-*mos* and RT7

Joy Richman, Ph.D., *Department of Anatomy, University of Manitoba* bFGF & Retinoic Acid: Roles in Development of the Embryonic Chick Face

Robert Hudziak, *Genentech Inc., San Bruno, California* HER2/c-erbB-2-NEU Gene: Role in Oncogenesis and Potential Therapies

MOLECULAR ONCOLOGY

Senior Members

Arnold H. Greenberg, M.D. , Ph.D.
Michael Mowat, Ph.D.
Eva A. Turley, Ph.D.
Jim Wright, Ph.D.

Research Associates and Postdoctoral Fellows

Francis Amara, Ph.D.
Aiping Huant, Ph.D.
Shanti Samuel, Ph.D.
Maureen Spearman, Ph.D.
Pardeep Bhatia, Ph.D.
Roberty Hurta, Ph.D.
Lois Schwarz, Ph.D.
Euan Taylor, Ph.D.

Graduate Students

Asim Ashique, B.Sc.
Yonhzhong Chen, B.Sc.
Bob Choy, B.Sc.
Jacqueline Damen, B.Sc.
Christine Hall, B.Sc.
Yang Ping, M. Sc.
Wenzheng Yang, B.Sc.
Racquel Baert, B.Sc.
Christine Chiu, B.Sc.
Genevieve Curpen, B.Sc.
Deng Feng, M.Sc.
Geoffrey Hicks, B.Sc.
William Taylor, B.Sc.

Summer Students

Racquel Baert
Anne Robbins
Gavin MacBeath
Pasul Syslak

Technicians

Arthur Chan
Paul Moreira
Anne Robbins
Michael Talgoy
Valerie Cripps
Robert Myers
Mary Sauder

Research Reports

SECRETED PHOSPHOPROTEIN mRNA IS INDUCED DURING MULTI-STAGE CARCINOGENESIS IN MOUSE SKINAND CORRELATES WITH THE METASTATIC POTENTIAL OF MURINE FIBROBLASTS

Ann Marie Craig, G. Tim Bowden, Ann F. Chambers, Maureen A. Spearman, Arnold H. Greenberg, Jim A. Wright, Marilyn McLeod and David T. Denhardt.

Secreted phosphoprotein I (SPP), also known as 2ar, osteopontin, 44-kDa bone phosphoprotein, bone sialoprotein I, and transformation-related phosphoprotein, is a 41.5-kDa glycosylated phosphoprotein secreted by many mammalian cell lines and expressed in a limited set of tissues. Using a cNDA probe, we found that SPP mRNA, which is barely detectable in normal mouse epidermis, was expressed at moderate-to-high levels in 2 of 3 epidermal papillomas and at consistently high levels in 7 of 7 squamous-cell carcinomas induced by an initiation-promotion regimen. This contrasts with the transient induction we had previously observed after a single application of the tumor promoter 12-0-tetradecanoylphorbol-13-acetate (TPA). In a set of 5 independently isolated T24-H-*ras*-transfected mouse C3H 10T½ cell lines, the levels of SPP mRNA correlated well with ras mRNA levels and with both experimental and spontaneous metastatic ability. SPP mRNA expression was also elevated in a derivative of mouse LTA cells transfected with genomic DNA from B16F1 melanoma cells and selected for increased experimental metastatic ability in the chick embryo. This apparent association of SPP expression with invasion, progression and metastasis, along with the presence of a functional ArgGlyAsp (RGD) cell adhesion site in SPP (osteopontin), leads us to propose that SPP may act as an autocrine adhesion factor for tumor cells.

GROWTH FACTOR MODULATION OF METASTATIC LUNG COLONIZATION

Sean E. Egan, Lenka Jarolim, Snezna Rogelj, Maureen Spearman, Jim A. Wright, and Arnold H. Greenberg

Altered production and response to growth factors is often involved in neoplasia but little is known about their effect on the dissemination of tumors. Therefore, we have examined the effect of growth factors on metastatic lung colonization. Autocrine induction of the metastatic phenotype was demonstrated in NIH-3T3 cells transformed by a signal peptide-bFGF gene but not bFGF in the absence of the signal peptide. In addition, exogenous growth factor regulation of metastasis was demonstrated. Treatment of *ras* transformed C3H-10T½ cells and *ras* or *src* transformed NIH-3T3 cells with bFGF prior to intravenous injection resulted in potent inhibition of metastatic potential. Stimulation of v-*fms* transformed cells by the natural *fms*-ligand, CSF-1, resulted in potent stimulation of metastatic behavior in freshly plated or refed cells, whereas following autocrine conditioning of the medium, the metastatic properties of these cells were sensitive to inhibitory effects of CSF-1. These observations indicate that specific growth factors can regulate the metastatic phenotype and, depending on the oncogenes responsible for cell transformation and autocrine conditioning, these effects can be either stimulatory or inhibitory.

MOLECULAR DETERMINANTS OF METASTATIC TRANSFORMATION

Sean E. Egan, Jim A. Wright and Arnold H. Greenberg

The dissemination of cancer is a complex process requiring many specialized characteristics. In order for a tumor cell to metastasize it must have the ability to degrade extracellular matrix structures including basement membranes which line

Dr. Jm Wright and Ph.D. Student Christine Chiu

blood vessels and lymphatics. In addition, the metastatic cell must survive hydrostatic pressure drops in the microvasculature, immune surveillance, and finally possess the ability to bind to endothelium at the secondary site, extravasate out of the vessel and form an autonomous lesion. In the past, the metastatic cell has been viewed as one whose phenotype is extremely unstable. It was thought that through this instability the large number of phenotypic characteristics could be acquired by a single cell. Thus, the metastatic cascade was viewed as a stochastic process involving a large number of gene products. Highly malignant cells are often aneuploid and possess an unstable karyotype, however, it is difficult to imagine that the large number of properties required for metastasis could be achieved by a single cell if they were truly independent events. The effects of this genomic instability may be limited to relatively few genes that can regulate the metastatic phenotype. In this alternative model, instability facilitates tumor progression or evolution but the genes are regulatory and not a part of the ultimate metastatic phenotype. There are numerous experiments which demonstrate that many of these "metastatic properties" can be controlled through the same signal transduction pathways as growth and differentiation signals. Work over the last five years on the potential role of oncogenes in metastatic dissemination has provided evidence for this hypothesis.

Dr. Mike Mowat and his industrious students Nancy Stewart, Geoff Hicks and Asim Ashique

TRANSIENT ALTERATIONS IN THE EXPRESSION OF PROTEASE AND EXTRACELLULAR MATRIX GENES DURING METASTATIC LUNG COLONIZATION BY H-*ras* TRANSFORMED 10T½ FIBROBLASTS

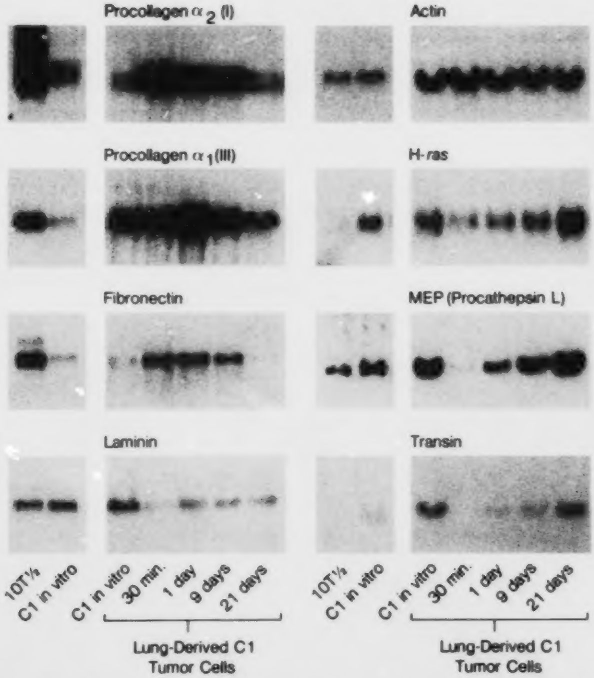
M.C. Gingras, L. Jarolim, G.T. Bowden, J.A. Wright, and A.H. Greenberg.

It has been proposed that tumor progression is a selective process and only a minority of tumor cells survive this selection because they possess the phenotypic traits necessary for metastasis and organ colonization. Both proteases and extracellular matrix proteins have been implicated in invasion and metastasis formation. To examine the nature of the selection process, we transformed 10T½ fibroblasts with T24 H-*ras* and the neo^R gene and selected a clonal line expressing the mutant ras gene. After intravenous injection of this line into syngeneic C3H/HeN mice, tumor cells were recovered from lungs by enzymatic treatment and selective outgrowth in G418. Less than 1 in 10^3 cells survived in the lung 30 min. after inoculation and these exhibited a unique phenotype. This was characterized by a propensity to lodge in the lung on reinjection, markedly enhanced mRNA levels of procollagenα_2(I), procollagenα_1(III) and fibronectin, and decreased levels of laminin, MEP (procathepsin L), transin and H-*ras*. Between 1 and 9 days after tumor injection, the phenotype of the cells surviving in the lung changed dramatically and exhibited a pattern of gene expression with increased protease and low matrix protein mRNA levels. This coincided with a 26-fold increase in the ability to colonize lungs on intravenous injection. Both the phenotype characterized by its propensity to arrest in the lung, and that showing enhanced metastatic ability were unstable on prolonged in vitro culture. We hypothesize that two selection events have occured. The first is for lung arrest and implantation of variants of the injected tumor with high matrix protein and low protease levels. A second selection then occurs for tumor cells that carry a favorable phenotype for invasion and proliferation which is associated with low matrix protein and high protease gene expression. These two phenotypes are represented within a clonal population of recently transformed tumor cells.

MUTANT p53 TUMOR SUPPRESSOR ALLELES RELEASE *ras*-INDUCED CELL CYCLE GROWTH ARREST

Geoffrey G. Hicks, Sean E. Egan, Arnold H. Greenberg, and Michael Mowat

Over expression of an activated *ras* gene in the rat embryo fibroblast line REF52 results in growth arrest at either the G1/S or G_2/M boundaries of the cell cycle. Both the DNA tumor virus proteins, SV40 large T antigen and Adenovirus 5 E1a, are able to rescue *ras* induced lethality and cooperate with *ras* to fully transform REF52 cells. In this report we present evidence that the wild-type activity of the tumor suppressor gene p53 is involved in the negative growth regulation of this model system. p53 genes encoding either a p53val^{135} or p53pro^{193} mutation express a highly stable p53 protein with a conformation dependent loss of wild-type activity and the ability to eliminate any endogenous wild-type p53 activity in a dominant-negative manner. In co-transfection assays these mutant p53 genes are able to rescue REF52 cells from *ras* induced growth arrest resulting in established cell lines which express elevated levels of the *ras* oncoprotein and show morphological transformation. Full transformation, as assayed by tumor formation in nude mice, is found only in the p53pro^{193}-plus-*ras* transfectants. These cells express higher levels of the *ras* protein compared to the p53val^{135}-plus-*ras* transfected cells. Transfection of REF52 cells with *ras* alone or afull length genomic wild-type p53-plus-*ras* results in growth arrest and lethality. Therefore, the selective event for p53 inactivation or loss during tumor progression may be to overcome a cell cycle restriction induced by oncogene overexpression (*ras*). These results suggest that a normal function of p53 may be to mediate negative growth regulation in response to *ras* or other proliferative inducing signals.



Progressive alterations in the expression of matrix and protease genes during lung colonization by metastatic ras-transformed 10T½ fibroblasts.

AMPLIFICATION OF THE GENES FOR BOTH COMPONENTS OF RIBONUCLEOTIDE REDUCTASE IN HYDROXYUREA RESISTANT MAMMALIAN CELLS

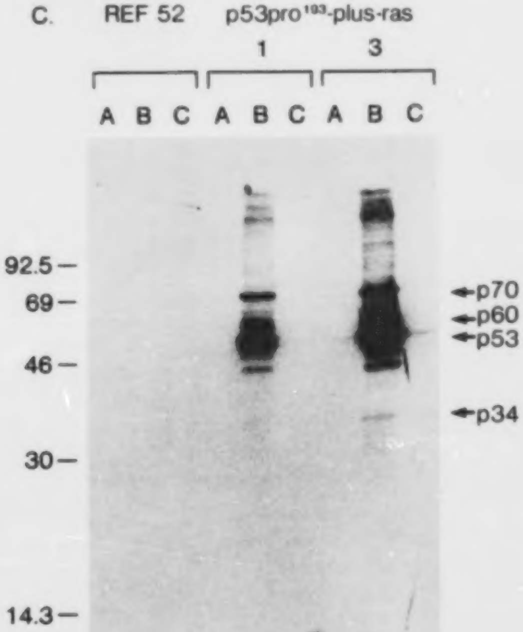
Robert A.R. Hurta and Jim A. Wright

Ribonucleotide reductase catalyzes the formation of deoxyribonucleotides from ribonucleoside diphosphate precursors, and is a rate-limiting step in the synthesis of DNA. The enzyme consists of two dissimilar subunits usually called M1 and M2. The antitumor agent, hydroxyurea, is a specific inhibitor of DNA synthesis and acts by destroying the tyrosyl free radical of the M2 subunit of ribonucleotide reductase. Two highly drug resistant cell lines designated H^R-15 and H^R-30 were isolated by exposing a population of mouse L cells to increasing concentrations of hydroxyurea. H^R-15 and H^R-30 cells contained elevated levels of ribonucleotide reductase activity, and were 68 and 103 times, respectively, more resistant than wild type to the cytotoxic effects of hydroxyurea. Northern and Southern blot analysis indicated that the two drug resistant lines contained elevated levels of M2 mRNA and M2 gene copy numbers. Similar studies with M1 specific cDNA demonstrated that H^R-15 and H^R-30 cell lines also contained increased M1 message levels, and showed M1 gene amplification. Mutant cell lines altered in expression and copy numbers for both the M1 and M2 genes are useful for obtaining information relevant to the regulation of ribonucleotide reductase, and its role in DNA synthesis and cell proliferation.

MAMMALIAN DRUG RESISTANT MUTANTS WITH MULTIPLE GENE AMPLIFICATIONS: GENES ENCODING THE M1 COMPONENT OF RIBONUCLEOTIDE REDUCTASE, THE M2 COMPONENT OF RIBONUCLEOTIDE REDUCTASE, ORNITHINE DECARBOXYLASE, p5-8, THE H-SUBUNIT OF FERRITIN, AND THE L-SUBUNIT OF FERRITIN

Robert A.R. Hurta and Jim A. Wright

Hydroxyurea was used to select two very highly drug resistant cell lines, designated H^R-15 and H^R-30. Both drug resistant lines contained elevated levels of ribonucleotide reductase activity. Northern and Southern blot analysis indicated that the two drug resistant lines contained increased levels of mRNA for the two components, M1 and M2, of ribonucleotide reductase, and M1 and M2 gene amplifications. Alterations in M1 and M2 protein levels were also evident in Western blot analysis. Further studies of H^R-15 and H^R-30 cells by Northern and Southern blot analysis showed that the drug resistant cell lines had elevated levels of ornithine decarboxylase mRNA and p5-8 mRNA, as well as increased ornithine decarboxylase and p5-8 gene copy numbers, respectively. Furthermore, characterization of H^R-15 and H^R-30 drug-resistant cell lines revealed increased mRNA levels for both H- and L-ferritin. Both cell lines exhibited by Southern blot analysis,



Expression of p53 tumor suppressor protein in the rat embryo fibroblast cell line REF 52, co-transfected with the ras oncogene and a mutant p53 gene. This figure shows several cellular proteins found associated with p53 in the immunoprecipitations. These proteins may be important for p53's tumor suppressing function.

amplificaton of the H- and L-ferritin genes. Increases in the cellular levels of H- and L-ferritin subunit proteins were also observed in both H^R-15 and H^R-30 cells, by Western blot analysis. This is the first description of mutant cell lines containing this complex combination of modified gene expressions and gene amplifications. The alterations exhibited by these lines confirm and extend present models of hydroxyurea resistance, are in agreement with and help substantiate models of ribonucleotide reductase regulation, and provide interesting links between the expressions of several cellular activities important in proliferation.

EXPRESSION OF WILD-TYPE p53 IS NOT COMPATIBLE WITH CONTINUED GROWTH OF p53-NEGATIVE TUMOR CELLS

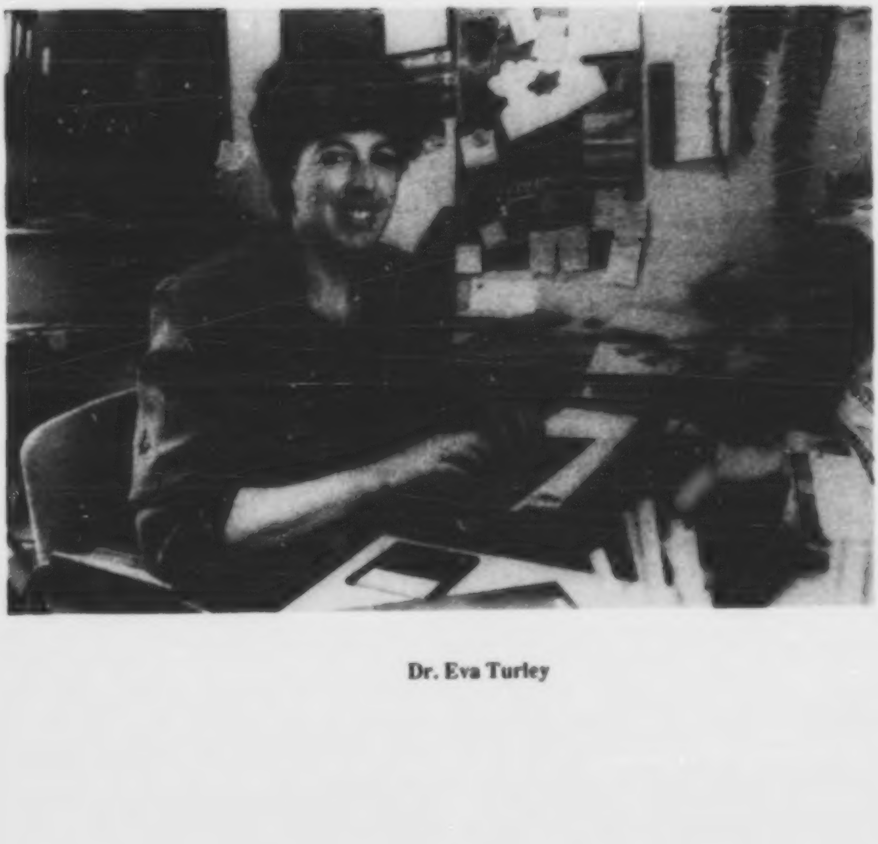
Penny Johnson, Dawn Gray, Michael Mowat, and Samuel Benchimol

Inactivation of the cellular p53 gene is a common feature of Friend virus-induced murine erythroleukemia cell lines and may represent a necessary step in the progression of this disease. As well, frequent loss or mutation of p53 alleles in diverse human tumors is consistent with the view of p53 as a tumor suppressor gene. To examine the significance of p53 gene inactivation in tumorigenesis, we have attempted to express transfected wild-type p53 in three p53-negative tumor cell lines: murine DP16-1 Friend erythroleukemia cells, human K562 cells, and SKOV-3 cells. We found that aberrant p53 proteins, which differ from wild-type p53 by a single amino acid substitution, were expressed stably in these cells, whereas wild-type p53 expression was not tolerated. The inability of p53-negative tumor cell lines to support long-term expression of wild-type p53 protein is consistent with the view that p53 is a tumor suppressor gene.

INCREASED FERRITIN GENE EXPRESSION IS ASSOCIATED WITH INCREASED RIBONUCLEOTIDE REDUCTASE GENE EXPRESSION AND THE ESTABLISHMENT OF HYDROXYUREA RESISTANCE IN MAMMALIAN CELLS

Grant A. McClarty, Arthur K. Chan, Bob K. Choy, and Jim A. Wright

In the present study, we show that hydroxyurea inactivated ribonucleotide reductase protein M2 has a destabilized iron centre, which readily releases iron. In addition, evidence is presented which indicates that single or multistep selection for hydroxyurea resistance, in a variety of mammalian cell lines, leads to alterations in the expression of the gene for the iron storage protein, ferritin. In all hydroxyurea resistant cell lines examined, including human, hamster, rat and mouse, there was an elevation in ferritin heavy (H) and/or light (L) mRNA levels but no change in the corresponding gene copy number. A detailed analysis of ferritin expression in a hydroxyurea resistant mouse L cell line showed that when compared to its wild type counterpart, there was an increase in H subunit concentration but no significant change in L subunit levels. The increased H/L subunit ratio was not brought about by specific changes in the rates of ferritin subunit biosynthesis, but rather resulted from changes in the post-translational stability of H subunits relative to L subunits in the resistant cell line compared to its parental wild type. Also, we show that treatment of cells with hydroxyurea results in an increased rate of ferritin biosynthesis in the absence of changes in H or L-mRNA levels. These results indicate that the development of even low level hydroxyurea resistance in mammalian cells may require alterations in ferritin gene expression, and they show an interesting relationship between the expressions of two highly regulated activities, ribonucleotide reductase and ferritin.



Dr. Eva Turley

RELATIONSHIP BETWEEN HEPARANASE ACTIVITY AND INCREASING METASTATIC POTENTIAL OF FIBROBLASTS TRANSFECTED WITH VARIOUS ONCOGENES

Lois C. Schwarz, Takatoshi Inoue, Tatsuro Irimura, Jacqueline E. Damen, Arnold H. Greenberg, and Jim A. Wright

We have examined the effects of transformation by activated H-*ras* and other transforming oncogenes on the activity of the enzyme, heparanase. Degradation of ^{3}H-N-acetylated-partially N-desulfated heparan sulfate by cellular extracts of the transformants was assesed by gel permation chromatography. More extensive degradation was observed with 10T½ mouse embryo fibroblasts transfected with an activated H-*ras* oncogene. The cells having the highest metastatic potential (CIRAS-3) were shown to contain the greatest heparanase activity, giving 49% higher levels of activity than parental cells ($p < 0.0002$). Furthermore, the enzyme activity produced by a series of H-*ras* transformed cell lines increased progressively with metastatic potential (non-parametric rank correlation coefficient $r = 0.96$). Transfection of NIH 3T3 fibroblasts with activated H-*ras*, v-*src* or v-*fes* oncogenes, which induced the metastatic phenotype, did not lead to large increases in heparanase activities. Also, inhibition of *ras*-induced malignancy by cotransfection of rat REF cells with the Ad2 E1a oncogene did not produce significant declines in heparanase activities. These results are consistent with the view that modifications in heparanase activity can play a role in the complex process of metastasis in some, but not all situations.

ABERRANT TGF-β PRODUCTION AND REGULATION IN METASTATIC MALIGNANCY

Lois C. Schwarz, Jim A. Wright, Marie-Claude Gingras, Paturu Kondaiah, David Danielpour, Mark Pimentel, Michael B. Sporn and Arnold H. Greenberg

We have examined the possible role of transforming growth factor-β (TGF-β) in metastatic malignancy by analyzing the production and activation of TGF-β_1 and β_2 and the regulation of TGF-β responsive genes in oncogene-transformed metastatic fibrosarcomas. All transformed lines derived from either 10T½ or NIH 3T3 by either H-ras or protein-kinase encoding oncogenes produced more TGF-β than parental cells. However, only highly metastatic fibrosarcomas secreted activated TGF-β at rates that were greater than parental fibroblasts. Immunohistochemical staining for TGF-β_1 showed widespread intracellular and extracellular distribution in metastatic lung nodules and adjacent tissue. Cells isolated from tumors successfully metastasizing to the lung had TGF-β_1 mRNA levels which were increased 19-fold over *in vitro* controls. Despite the greatly enhanced rate of secretion of activated TGF-β_1 metastatic cells exhibited markedly altered responses to TGF-β_1 and TGF-β_2, being unable to either increase collagen secretion or enhance collagen a2(I) or TGF-β_1 mRNAlevels. This lack of response was not due to either altered TGF-β receptor affinity or numbers. Metastatic progression was, therefore, associated with an increase in the secretion of activated TGF-β_1 and a loss of the ability to deregulate TGF-β-responsive genes.

ENHANCED SECRETION OF ACTIVATED TGF-β_1 AND POST RECEPTOR BLOCKADE TO TGF-β_1 SIGNALLING IN HIGHLY MALIGNANT FIBROSARCOMAS

Lois C. Schwarz, Jim A. Wright, Alice Hall, Mark Pinentel, Arthur Chan, Micheal Sporn and Arnold H. Greenberg

TGF-β is a member of an expanding family of homologous proteins required for the development, growth and differentiation of various normal mesenchymal, endothelial and epithelial cells. TGF-β is also implicated in uncontrolled proliferation since transformed cells can produce enhanced levels of TGF-β while often losing their sensitivity to its growth-suppressive effects. We questioned whether TGF-β was necessary for metastasis by determining the regulation of TGF-β expression, and response to TGF-β, in cells which vary in their malignant properties. To assess whether TGF-β expression was modified, the production and activation of TGF-β were examined in oncogene-transfected metastatic and non-metastatic fibrosarcomas derived from 10T• and NIH 3T3 cell lines. All transformed and metastatic cells produced more TGF-β than parental cells. However, only highly metastatic cell lines produced more activated TGF-β at rates of production that were greater than parental fibroblasts. This increase was observed regardless of cell origin or the oncogenes used to induce metastasis, suggesting that altered TGF-β expression is required for malignancy. Total deregulation of TGF-β expression was also indicated by an isotype-switch where metastatic 10T• lines produced predominantly TGF-β_1 while parental and non-metastatic transformed lines secreted TGF-β_2. Furthermore, the steady-state levels of TGF-β_1 mRNA in metastatic fibroblasts were elevated over non-metastatic controls.

To determine whether the response of TGF-β was modified in metastatic cells, the production of collagen in the presence of TGF-β was measured as well as the induction of genes normally regulated by TGF-β. Metastatic cells from the two independent series of cell lines were insensitive to TGF-β_1 as determined by their inability to increase collagen secretion. Highly metastatic CIRAS-3 cells were very poor responders yielding 7-fold less collagen than the parental 10T• line and 5-fold less than non-metastatic MDS.R5 cells. Similar results were obtained using TGF-β_2. The metastatic NIH 3T3 transformants were also unresponsive to 5.0 pM TGF-β_1, secreting collagen at 3 to 6-fold lower levels in the v-*src*, v-*fes* and A-*raf* derived lines than 3T3 cells. This lack of sensitivity was not observed in v-*myc* transfected NIH 3T3 or 10T• cells which responded well to 5.0 pM TGF-β_1. TGF-β_1 did not increase expression of procollagen α2(I) or TGF-β_1 mRNA in metastatic fibroblasts, in contrast to non-metastatic cells. This lack of response was not due to altered receptor affinity or numbers. Thus, malignant progression is associated with an increase in secretion of activated TGF-β and loss of responsiveness to TGF-β. Since receptor binding is not modified, this is likely a result of altered post-receptor transduction or integration of signals induced by TGF-β.

A HYALURONAN-BINDING PROTEIN SHOWS A PARTIAL AND TEMPORALLY REGULATED CODISTRIBUTION WITH ACTIN ON LOCOMOTING CHICK HEART FIBROBLASTS.

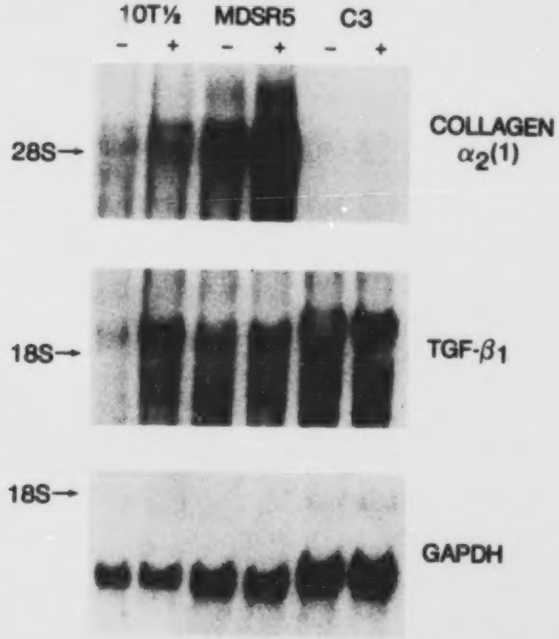
E.A. Turley, P. Brassel and D. Moore.

The ultrastructural distribution of a hyaluronan-binding protein (HABP) and its relationship to actin-containing microfilaments were studied with immunocytochemistry. Ultrastructural analysis localized HABP to the cell coat and demonstrated that it occurred largely in cell processes where the apical surfaces were immunopositive. The codistribution of HABP with actin-containing microfilaments in cell processes was demonstrated with double immunolabelling using monoclonal antibodies to actin and monospecific, polyclonal antibodies to HABP. Both the topological localization of HABP and its cytoskeletal coassociations were modulated by cells during different cellular phases. Thus, in cells exhibiting large lamellae and few actin fibrils, typical of rapidly locomoting cells, HABP codistributed primarily with the actin meshwork occurring in cell processes, although some codistribution between the two proteins occurred over the cell body. In cells containing prominent stress fibers and less obvious lamellae, HABP was absent in cell processes but, rather, was aligned primarily along actin fibrils occurring in the cell body. A functional association between HABP and the actin-containing cytoskeleton was suggested by the ability of cytocholasin D to coordinately alter the distribution of HABP and disrupt its coassociation with actin. As well, the addition of hyaluronan to monolayers increased the association of HABP with a Triton-insoluble cytoskeleton. The possible roles of HABP in cell motility and cytoskeletal organizations are discussed.

STUDIES ON THE EFFECT OF KETOCONAZOLE ON THE FUSION OF L6 MYOBLASTS

Stephen W[illegible]ne, James C. Jamieson, Maureen A. Spearman and Jim A. Wright

The multinucleated muscle fiber is formed from myotubes through the fusion of mononucleated myoblasts. The fusion reaction is accompanied by biochemical differentiation resulting in increases in the levels of a number of muscle specific proteins, such as creatine phosphokinase, adenylate kinase, acetylcholinesterase, glycogen phosphorylase and myosin. Several studies have implicated glycoproteins as mediators of myoblast recognition and adhesion events. In our own work a genetic approach has been used to study the involvement of surface glycoproteins in myogenesis. We have isolated con A-resistant L6 myoblast cell lines which we have used as a model system for studies of a pleiotropic mutation which results in cells containing modified cellular membranes. The Con A-resistant cells have lost the ability to undergo normal morphological or biochemical differentiation. These cells are believed to be defective in a mannosyl transferase activity responsible for transfer of mannose from Dol-P-Man to form high mannose containing lipid-oligosaccharides. The cells are thus unable to manufacture cell membrane glycoproteins containing oligosaccharide chains of the high mannose type. Moreover, studies in our laboratories and by oth-



Effect of TGF-β_1 on procollagen a2(1) and TGF-β_1 mRNA expression. Subccnfluent 10T·, MDS-R5, and CIRAS-3 cells were exposed to medium with 100 pm TGF-β_1 (+) or without TGF-β_1 (-) for 18 hr in DM. Total cellular RNA was isolated and probed for procollagen a2(1), TGF-β_1 and GAPDH mRNA. The 28S and 18S ribosomal RNA are indicated.

ers have led to the identification of cell surface glycoproteins which are believed to be fusogenic glycoproteins and which are defective in conA-resistant myoblasts. In support of the involvement of glycoproteins in myogenesis we have recently described the use of oligosaccharide processing inhibitors to modify cell membrane oligosaccharide structure in L6 myoblasts and we have correlated the structural changes with changes in the fusion reaction. Only processing inhibitors that altered the structure of oligosaccharide chains of the high mannose type of oligosaccharide inhibited the fusion reaction; similar results have been reported by others. Inhibition of fusion by the processing inhibitors was accompanied by a reduction of the activity of creatine phosphokinase showing that biochemical differentiation was also inhibited in presence of these compounds.

In order to further investigate the importance of cell membrane glycoproteins in the fusion reaction, this paper describes the use of ketoconazole, an inhibitor of HMG-CoA reductase, as a fusion inhibitor. HMG-CoA reductase is a key enzyme in the pathway leading to the synthesis of Dol-P. Since fusion of L6 myoblasts is particularly sensitive to alterations in cell surface oligosaccharides any modification in the formation of dolichol intermediates of glycoprotein biosynthesis would be expected to affect the fusion reaction. The results show that low concentrations of ketoconazole are very inhibitory for myoblast fusion; moreover, lack of fusion was found to correlate with an inhibition of biochemical differentiation as illustrated by reduced creatine phosphokinase activities. In addition, cell surface glycoprotein synthesis was inhibited as illustrated by reduced lectin binding to the cell surface coupled with inhibition of formation of lipid-oligosaccharide intermediates required for glycoprotein biosynthesis.

The results provide further evidence to support the concept that oligosaccharide chains of the N-linked type on cell membranes are important for the cell recognition process leading to myoblast fusion.

Immunofluorescent localization of HABP in (a) uninduced and (b) zinc-induced 212 cells. HABP was located on 212 cells by indirect immunofluorescence 24 h after induction of mutant hybrid ras gene or exposure to buffer, HABP was present in both cell populations, particularly in the cell processes. Between 4-24 h after induction, increased amounts of HABP were observed. This occurred as both amorphous and granular staining over the cell body. Bar, 2.8 µm.

REGULATION AND DRUG RESISTANCE MECHANISMS OF MAMMALIAN RIBONUCLEOTIDE REDUCTASE, AND THE SIGNIFICANCE TO DNA SYNTHESIS

Jim A. Wright, Arthur K. Chan, Bob K. Choy, Robert A.R. Hurta, Grant A. McClarty and Aaron Y. Tagger

Mammalian ribonucleotide reductase is a highly controlled enzyme activity, which occupies a key position in the synthesis of DNA, because it is soley responsible for the *de novo* reduction of ribonucleoside diphosphates to their corresponding deoxyribonucleoside diphosphate forms, required for DNA synthesis. Ribonucleotide reductase consists of two dissimilar protein components often called M1 and M2, which are independently regulated during cell proliferation. The M1 component contains multiple effector binding sites and is responsible for the complex allosteric regulation of the enzyme, whereas the M2 protein contains non-heme iron and a unique tyrosyl free radical required for ribonucleotide reduction. Since the reaction is rate-limiting for DNA synthesis, ribonucleotide reductase plays an important role in regulating cell division, and hence, cell proliferation. There are many inhibitors of ribonucleotide reductase and perhaps the most valuable one from a cell biology, biochemistry, and clinical point of view is the hydroxamic acid, hydroxyurea. This drug has also been very useful as a selective agent for isolating a variety of mammalian mutant cell lines altered in ribonucleotide reductase gene expression. Regulatory, structural and biological characteristics of ribonucleotide reductase have been reviewed (Biochem. Cell Biol., 68: 1364,1990), including evidence that ribonucleotide reductase, particularly the M2 protein has an important early role to play in tumor promotion. In addition, modifications in the expressions of genes altered in hydroxyurea resistant mutants cultured in the absence or presence of hydroxyurea were discussed in the review noted above, with emphasis on changes in M2 protein, M1 protein and the iron storage protein ferritin. Several regulatory models were presented, including a model showing the relationships between M2 protein levels, deoxyribonucleotide pools and DNA synthesis, and a model demonstrating a linkage between M2 and ferritin proteins in regulating DNA synthesis in normal and hydroxyurea resistant mammalian cells.

GENETIC REGULATION OF METASTATIC PROGRESSION

Jim A. Wright, Sean E. Egan and Arnold H. Greenberg

Metastasis is a complex process that results in tumor growth sites distant from the primary neoplasm. The spread of cancer is responsible for the majority of cancer deaths because conventional therapy is frequently unsuccessful in the treatment of widely disseminated disease. Clearly, it is important to understand the properties of malignant metastatic cells which distinguish them from benign tumor cells. The metastatic process is very complex since metastatic cells must dissociate from the primary tumor, intravasate into the vasculature or lymphatics, survive potential immune attack and hydrodynamic pressure drops in the vasculature, bind to endothelium, extravasate into the surrounding tissue, and eventually develop into an autonomous tumor. Some studies have suggested thatthe phenotypic properties of a metastatic cell are very unstable, and that this instability is important in mechanisms responsible for generating metastatic variants characterized by the wide variety of altered biological properties. Hypotheses have been presented in an attempt to explain the complex metastatic cascade, and many of them propose that a large number of independent random genetic and/or epigenetic alterations are responsible for the various changes in biological properties. However, it now appears that many of the modified properties of metastatic populations are not necessarily acquired or regulated independently, but may instead be controlled through modification in expression of a relatively small number of key genes. These genes are normally essential for the regulation of diverse cellular functions including proliferation, differentiation, cell-cell communication and

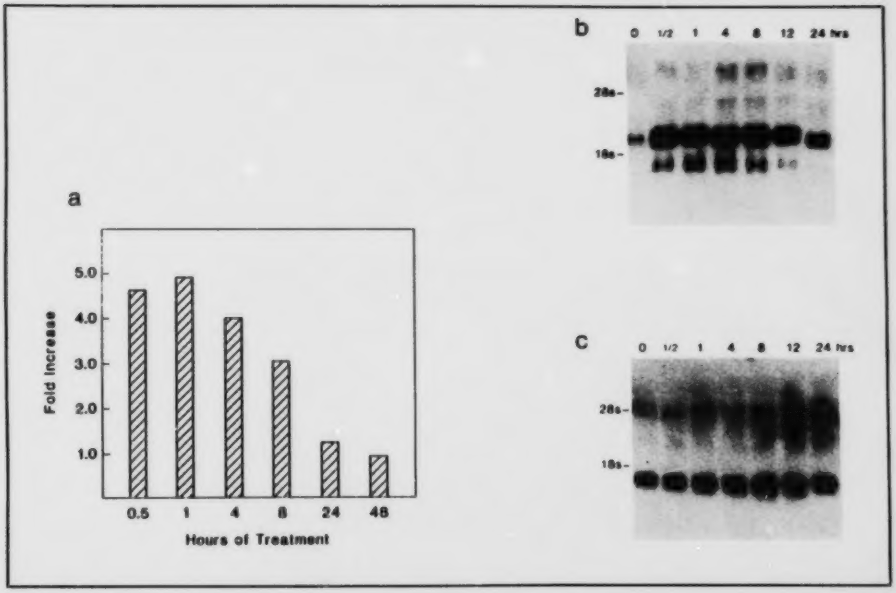
Dr. Arnold Greenberg discussing an experiment with graduate student Ricky Kraut

motility. In addition, many of these genes, when altered, play a role in malignant transformation, and frequently are referred to as cellular oncogenes and tumor suppressor genes. In a recent review article (Anticancer Res., 10:1247, 1990), we have examined our investigations into the role that oncogenes play in the metastatic spread of tumor cells in experimental animal systems. Particular attention was given to investigations of the ras oncogenes, with brief discussions on related aspects of altered growth factor regulation, tumor suppressor genes and gene complementation.

DNA AMPLIFICATION IS RARE IN NORMAL HUMAN CELLS

Jim A. Wright, Helene S. Smith, Fiona M. Watt, Miriam C. Hancock, David L. Hudson, and George R. Stark

Three types of normal human cells were selected in tissue culture with three drugs without observing a single amplification event from a total of 5×10^8 cells. No drug-resistant colonies were observed when normal foreskin keratinocytes were selected with N-(phosphonacetyl)-L-aspartate or with



Rapid elevation of ribonucleotide reductase activity with BALB/c 3T3 cells, within 30 min. of treatment with 0.1 μM TPA (a). Northern blot analysis of the M2 component of ribonucleotide reductase showed a marked transient elevation of M2 mRNA after 30 min. of TPA treatment (b). Northern blot analysis of glyceraldehyde-3-phosphate dehyxrogenase mRNA levels are shown as a control for loading (c). These results suggest that the ribonucleotide reductase M2 component plays an important role in the critical early events involved in the process of tumor promotion.

hydroxyurea or when normal mammary epithelial cells were selected with methotrexate. Sime slightly resistant colonies with limited potential for growth were obtained when normal diploid fibroblast cells derived from fetal lung were selected with methotrexate or hydroxyurea but DNA amplification in normal human cells contrasts strongly with the situation in tumors and in established cell lines, where amplification of oncogenes and the genes mediating drug resistance is frequent. The results suggest that tumors and cell lines have acquired the abnormal ability to amplify DNA with high frequency.

Publications

Craig, A.M., Bowden, G.T., Chambers, A.F., Spearman, M.A., Greenberg, A.H., Wright, J.A., McLeod, M. and Denhardt, D.T. Secreted phosphoprotein mRNA is induced during multi-stage carcinogenesis in mouse skin and correlates with the metastatic potential of murine fibroblasts. Int. J. Cancer, 46:133-137, 1990.

Egan, S.E., Jarolim, L., Rogelj, S., Spearman, M., Wright, J.A. and Greenberg, A.H. Growth factor modulation of metastatic lung colonization. Anticancer Res., 10:1341-1346, 1990.

Egan, S.E., Wright, J.A. and Greenberg, A.H. Molecular determinants ofmetastatic transformation. Environ. Health Perspectives, 93:91-95, 1990

Gingras, M-C., Jarolim, L., Finch, L., Bowden, G.T., Wright, J.A. and Greenberg, A.H. Transient alterations in the expression of protease and extracellular matrix genes during metastatic lung colonization by H-ras-transformed 10T• fibroblasts. Cancer Res., 50:4061-4066, 1990.

Hurta, R.A., Wright, J.A. Mammalian drug resistant mutants with multiple gene amplifications: genes encoding the M1 component of ribonucleotide reductase, the M2 component of ribonucleotide reductase, ornithine decarboxylase, p5-8, the H-subunit of ferritin and the L-subunit of ferritin. Biochim. Biophys. Acta, 1087:165-172, 1990.

Hurta, R.A. and Wright, J.A. Amplification of the genes for both components of ribonucleotide reductase in hydroxyurea resistant mammalian cells. Biochem. Biophys. Res. Commun., 167:258-264, 1990.

Johnston, J.B., Israels, L.G., Goldenberg, G.J., Anhalt, C.D., Verburg, L., Mowat, M.R.A., and Begleiter, A. Glutathione S-transferase, sulfhydryl groups and DNA crosslinking activity with chlorambucil in chronic lymphocytic leukemia. J. Natl. Cancer Inst. USA, 82:776-779, 1990.

Clarty, G.A., Chan, A.K., Choy, B.K. and Wright, J.A. Increased ferritin gene expression is associated with increased ribonucleotide reductase gene expression and the establishment of hydroxyurea resistance in mammalian cells. J. Biol. Chem., 265:7539-7547, 1990.

Mowat, M., Sauder, M., and Pereira, D. The activated form of p53 is not a transactivator of the Intracisternal A Particle long terminal repeat. Oncogene, 5:241-244, 1990.

Schwarz, L.C., Inoue, T., Irimura, T., Damen, J.E., Greenberg, A.H. and Wright, J.A. Relationships between heparanase activity and increasing metastatic potential of fibroblasts transfected with various oncogenes. Cancer Letters, 51:187-192, 1990.

Schwarz, L.C., Wright, J.A., Hall, A., Pimentel, M., Chan, A., Sporn, M.and Greenberg, A.H. Enhanced secretion of activated TGF-β_1 and post receptor blockade to TGF-β_1 signalling in highly malignant fibrosarcomas. Annals of N.Y. Acad. Sci., 593:315-317, 1990

Schwarz, L.C., Wright, J.A., Gingras, M-C., Kondaiah, P., Danielpour, D., Pimentel, M., Sporn, M.B. and Greenberg, A.H. Aberrant TGF-β production and regulation in metastatic malignancy. Growth Factors, 3:115-127, 1990.

Turley, E.A., Brassel, P. and Moore, D. A hyaluronan-binding protein shows a partial and temporally regulated codistribution with actin on locomoting chick heart fibroblasts. Exp. Cell Res., 187:243-249, 1990.

Wayne, S., Jamieson, J.C., Spearman, M.A. and Wright, J.A. Studies on the effect of ketoconazole on the fusion of L6 myoblasts. Mol. Cell. Biochem., 92:137-146, 1990.

Wright, J.A., Chan, A.K., Choy, B.K., Hurta, R.A.R., McClarty, G.A. and Tagger, A.Y. Regulation and drug resistance mechanisms of mammalian ribonucleotide reductase, and the significance to DNA synthesis. Biochem. Cell Biol., Accepted, 1990.

Wright, J.A., Egan, S.E. and Greenberg, A.H. Genetic regulation of metastatic progression. Anticancer Res., 10:1247-1256, 1990.

Wright, J.A., Smith, H.S., Watt, F.M., Hancock, M.C., Hudson, D.L. and Stark, G.R. DNA amplification is rare in normal human cells. Proc. Natl. Acad. Sci. USA, 87:1791-1795, 1990.

Published Abstracts

Choy, B.K., McClarty, G.A. and Wright, J.A. Phorbol ester induction of ribonucleotide reductase. UCLA Symposium on Molecular and Cellular Biology. J. Cell. Biochem., 14B:192, 1990.

Greenberg, A.H., Schwarz, L.C., Gingras, M-C., Kondaiah, P., Danielpour, D., Sporn, M.B. and Wright, J.A. Aberrant TGF-β regulation in metastatic malignancy. UCLA Symposium on Molecular and Cellular Biology, J. Cell. Biochem., 14C:295, 1990.

Hurta, R.A.R. and Wright, J.A. Amplification of genes for both components of ribonucleotide reductase in hydroxyurea resistant mammalian cells. ASCB/EMBO Conference in the Cell Cycle, 40A, 1990.

Turley, E.A., Austen, L., Vandeligt K. and Clary, C. J. Cell. Biochem. Suppl. 14A, 130A, 1990.

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Research Reports

MECHANISMS OF RESISTANCE TO CHLORAMBUCIL IN CHRONIC LYMPHOCYTIC LEUKEMIA

Asher Begleiter, Gerald J. Goldenberg, Cynthia D. Anhalt, Kristine Tang, Michael R.A. Mowat, Lyonel G. Israels, and James B. Johnston

Chronic lymphocytic leukemia is most frequently treated with the alkylating agent chlorambucil and approximately 60% of previously untreated patients respond to this therapy, although most subsequently become refractory to this agent. In the present study we examined the biochemical mechanisms responsible for resistance to chlorambucil in this disease. The formation and repair of DNA crosslinks was measured in lymphocytes from patients following in vitro treatment with 100 mM chlorambucil, and these factors were correlated with the clinical responses of the patients, as measured by the percent fall in lymphocyte count following treatment with chlorambucil (0.9 mg/kg, given over 3 days). In addition, the levels of sulfhydryl compounds and glutathione S-transferase activity in these cells were correlated with response to treatment. Of eighteen patients studied, five had been treated with chlorambucil previously while thirteen had received no prior treatment. Six of the patients were responsive to treatment while twelve failed to respond. We observed no correlation between response to chlorambucil treatment and the rate of crosslink formation, the maximum level of DNA crosslinks, the residual level of crosslinks after 22 h, the percent or rate of crosslink repair, and the area under the crosslink versus time curve. In addition, there were no significant differences for any of the pharmacological parameters between sensitive and resistant or between previously treated and untreated patients. We also observed no correlation between clinical response to treatment and the level of total sulfhydryls, non protein-bound sulfhydryls, protein-bound sulfhydryls, glutathione or glutathione S-transferase activity. However, a significant positive correlation was observed between the protein-bound sulfhydryl:glutathione ratio and clinical response. This finding suggests that glutathione may be related to chlorambucil resistance in chronic lymphocytic leukemia while protein-bound sulfhydryl compounds may serve as targets for the antineoplastic activity of this agent.

MECHANISMS FOR THE MODULATION OF ALKYLATING ACTIVITY BY THE QUINONE GROUP IN QUINONE ALKYLATING AGENTS

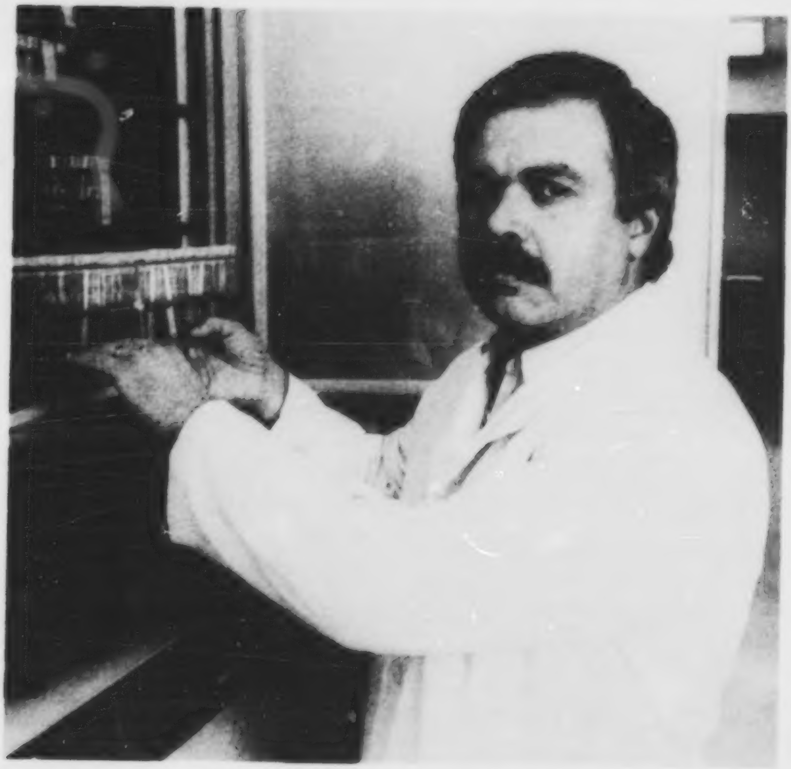
Asher Begleiter, Marsha K. Leith, and Su-Shu Pan

Previous studies have demonstrated that the quinone group may play an important role in modulating the alkylating activity of quinone alkylating agents. Introduction of a quinone moiety markedly increased the alkylating activity and cytotoxic activity of the model quinone alkylating agents, benzoquinone mustard and benzoquinone dimustard. However, the cytotoxic and DNA damaging activity of benzoquinone mustard was considerably greater than that of benzoquinone dimustard. In this study, we have investigated the role of the quinone group as a modulator of alkylating activity in these antitumor agents using extracellular assays to eliminate differences due to cellular drug uptake and metabolism. Evidence was obtained that the alkylating activities of both benzoquinone mustard and benzoquinone dimustard were enhanced by reduction of the quinone group. In addition, when these agents were reduced, they displayed equal alkylating activity. This finding suggests that the difference in the activity of these agents in cells is not due to intrinsic differences in alkylating activities of the activated forms of these agents. Electrochemical studies revealed that benzoquinone dimustard has a lower redox potential than benzoquinone mustard and thus is less easily reduced. Inactivation and spectroscopic studies suggested that a major reason for the differences in activity between benzoquinone mustard and benzoquinone dimustard may be the rapid inactivation of the dimustard prior to its reduction. This effect may be enhanced by the lower redox potential of benzoquinone dimustard compared with benzoquinone mustard. These findings support the hypothesis that the quinone group can modulate the alkylating activity of quinone alkylating agents; however, the mechanisms by which this modulation occurs may vary for different antitumor agents.

STUDIES OF COMBINATION THERAPY WITH dCF/dAdo AND BLEOMYCINS

Asher Begleiter, Heather Peniuk, and James B. Johnston

The bleomycins are an important group of natural product antitumor agents that are effective in the treatment of testicular carcinoma, squamous cell carcinomas and lymphoid malignancies. Their cytotoxic action appears to be due to their ability to cause DNA strand breaks (SB) and fragmentation. Bleomycin causes DNA SB by interacting with oxygen and ferrous or cupric ions to form oxygen-free radicals. This is similar to the mechanism proposed for the cytotoxic effects of radiation. Like dCF, bleomycin is relatively non-myelosuppressive and thus might be useful in combination with dCF for treating lymphomas, where there is extensive marrow packing. Since we have previously observed a synergistic antitumor effect by combining dCF/dAdo with radiation, as a result of inhibition of repair of radiation-induced DNA SB, we examined whether a similar increase in activity could be achieved by combining dCF/dAdo with bleomycin. DNA SB



Dr. Asher Begleiter

were measured by alkaline elution following 2 hr treatment of plateau-phase L5178Y murine lymphoblasts with 200 mM bleomycin to measure the formation and repair of these lesions in the absence or presence of dCF/dAdo. Bleomycin treatment produced more than 200 rad equivalents of DNA SB; however, more than 80% of these breaks were repaired within 6 hr. As previously observed with radiation, dCF/dAdo inhibited the repair of DNA SB induced by bleomycin. The cytotoxic activity of bleomycin was compared in plateau-phase L5178Y murine lymphoblasts in the absence or in combination with dCF (5 mM) and dAdo (50 mM) using clonogenic assays. The results indicate that the combination therapy is more effective than either bleomycin or dCF/dAdo alone. However, it is not clear yet from these results whether the addition of dCF/dAdo with bleomycin produces a synergistic antitumor effect. We are continuing our studies of combination therapy with bleomycin and dCF/dAdo to confirm our initial results and to optimize both the scheduling and dose levels of this combination of agents. These studies will help us determine if the use of dCF, together with bleomycin, might be useful in the clinic for the treatment of lymphoid malignancies.

EFFECT OF TRANSFORMING GROWTH FACTOR–β ON DNA SYNTHESIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

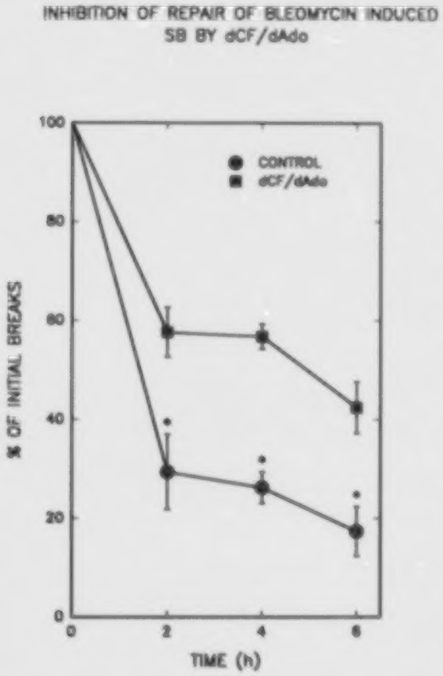
Lyonel G. Israels, Sara Israels, Michael I. Jesson, Lois Schwartz, Asher Begleiter, Michael R. A. Mowat, Michael B. Sporn, and James B. Johnston

Transforming growth factor-β (TGF-β) is an important immunoregulator of human B and T lymphocytes, as it down-regulates T cell clonal expansion, B cell proliferation and immunoglobulin secretion. In the present study we have examined the localization of TGF-β in B cells from normal donors and patients with chronic lymphocytic leukemia (CLL) and have assessed the influence of TGF-β_1 on DNA synthesis in these cells. Using anti-LC(1-30), a polyclonal anti-TGF-β_1 antibody, TGF-β was localized to discrete sites within the cytoplasm of both normal and malignant lymphocytes. These areas colocalized with an antigranular antibody (D545), suggesting that TGF-β may be stored within cytoplasmic granules. DNA synthesis, as measured by $[^3H]$thymidine incorporation, was reduced to a mean ± SE of control of 0.84 ± 0.07 in CLL cells from 18 patients and this was significantly less ($p < 0.001$) than that observed in the B cells of 14 normals (mean ± SE of control, 0.42 ± 0.04). In 3 of the 18 patients, TGF-β_1 actually stimulated DNA synthesis. A significant inverse correlation was observed between baseline DNA synthesis and the inhibition of this activity by TGF-β, in both normal ($p < 0.01$), and CLL ($p < 0.001$) cells. This relationship may help explain the reduced effect of TGF-β on the leukemic cells, as the baseline level of DNA synthesis was lower in CLL cells than in normals. The loss of down-regulation by TGA-B in CLL may, in part, account for the uncontrolled proliferation of the leukemic B cell population in this disease.

TRANSFORMING GROWTH FACTOR-β IN MYELOFIBROSIS

James B. Johnston, Ginette Michaud, Sara J. Israels, Bakul I. Dalal, Asher Begleiter, Lyonel G. Israels, and Arnold H. Greenberg

Transforming growth factor-beta (TGF-β) was demonstrated by immunohistochemistry to be present in the marrow biopsies of five patients with myelofibrosis of different etiologies. The extent of TGF-β deposition paralleled the severity of marrow fibrosis and no TGF-β was detected in marrows without fibrosis. By immunfluorescence, TGF-β was detected in discrete sites in the cytoplasm of immature and mature myeloid cells and large granular lymphocytes (LGL), and these sites colocalized with areas detected by an antigranule antibody, suggesting that TGF-β may be stored within granules. Compared to normal T cells, the cells of two patients with large granular lymphocytic leukemia secreted the high levels of TGF-β, with the level paralleling the extent of TGF-deposition of marrow fibrosis. Thus, myelofibrosis may occur as a result of TGF-β release in the marrow and leukemic cells may be a source of this cytokine.



Cells were incubated with or without dCF/dAdo and DNA strand breaks were measured at various times. The figure shows that cells incubated with dCF/dAdo repair DNA strand breaks less efficiently than control cells

THE ROLE OF DT-DIAPHORASE (DT) IN MITOMYCIN C (MMC) ACTIVATION UNDER AEROBIC AND HYPOXIC CONDITIONS.

Marsha K. Leith, Erica Robotham, and Asher Begleiter.

DT catalyzes two electron reduction of quinones to the hydroquinone and has been implicated in activation of MMC alkylating activity. We investigated the role of DT in activating MMC under aerobic and hypoxic conditions by comparing the activity of this agent in L5178Y (LY) lymphoblasts, which have low DT activity and L5178Y/HBM10 (HBM) cells, which have elevated DT activity. MMC produced increased cytotoxic and DNA crosslinking activity in HBM cells compared to LY cells under aerobic conditions. Although MMC activity was increased in LY cells under hypoxic conditions, hypoxia had little effect on MMC activity in HBM cells. The DT inhibitor, dicoumarol (DIC) decreased MMC activity in HBM cells under aerobic conditions, but had no effect under hypoxic conditions. DIC had no effect on MMC activity in LY cells under either aerobic or hypoxic conditions. These studies suggest that DT may play an important role in MMC activation under aerobic conditions, where levels of the more active MMC semiquinone may be low due to back oxidation, but may have little effect under hypoxia.

ELEVATED EXPRESSION OF THE c-*fes* PROTO-ONCOGENE IN ADULT HUMAN MYELOID LEUKEMIA CELLS IN THE ABSENCE OF GENE AMPLIFICATION.

T.E. Smithgall, J.B. Johnston, M. Bustin and R.I. Glazer

Expression of the 93-kd tyrosine kinase encoded by the human c-fes proto-oncogene (also known as FES) is restricted to mature hematopoietic cells of the granulocytic and monocytic lineages, suggestive of a function essential to normal myeloid differentiation. However, recent studies have shown that c-fes can transform fibroblasts if sufficient levels of gene expression are achieved.

These findings indicate that strict regulation of the c-fes gene is critical to normal myeloid development, whereas elevated c-fes expression may contribute to malignant transformation. In the present study, we compared the c-fes messenger RNA (mRNA) levels in leukemia blasts from patients with myeloid or lymphoid leukemia with those of peripheral monocytes from a normal donor with the use of a quantitative ribonuclease protection assay. The presence of c-fes mRNA was readily detected in both acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) cells, but c-fes mRNA was present in low levels or was absent in lymphoid leukemia cells. The leukemia cells of two of five AML patients and four of four CML patients expressed more c-fes mRNA than monocytes from a normal donor with more than a three-fold elevation in the cells of one CML patient. No evidence of amplification or rearrangement of the c-fes gene was detectable by Southern blot analysis of myeloid leukemia DNA, suggesting that the variation in c-fes mRNA levels are related to differences in transcriptional activity and/or message stability. These results indicate that elevated c-fes expression is a common feature of myeloid leukemia cells that could potentially contribute to the leukemia phenotype.

STUDIES OF THE PREVENTION OF DIABETES MELLITUS BY 2'-DEOXYCOFORMYCIN

J. Thliveris, A. Begleiter, N. Kobrinsky, H. Dean, and J. B. Johnston

There is compelling evidence that insulin-dependent diabetes mellitus (IDDM) is caused by autoimmune destruction of the pancreatic islet cells. In the genetically predisposed BB Wistar rat, an authentic model of IDDM, treatment with the immunosuppressive agent, cyclosporin, completely prevents the development of the disease. Though effective, cyclosporin is too nephrotoxic for long-term use. 2'-Deoxycoformycin (dCF) is a novel immunosuppressive agent that functions by inhibiting the enzyme adenosine deaminase (ADA). When used in low doses, the main side effects observed have included transient nausea, vomiting and lethargy. We have begun a study to evaluate the use of dCF in preventing and treating IDDM using the BB Wistar rat model. The BB Wistar rat developed by the Biobreeding Laboratories in Ottawa is a strain in which IDDM develops spontaneously in approximately 60-75% of the offspring of two diabetic parents at around 90 days of life. We have carried out several initial experiments to test the feasibility of the proposed hypothesis. At 30 days of life the animals were randomized into 3 groups, receiving either 0.5 mg/kg, 1.0 mg/kg, or 1.5 mg/kg dCF weekly, from 30 to 120 days, to evaluate the toxicity of the drug treatment. Animals which developed diabetes during the course of these studies were maintained with daily injections of insulin. As shown in the tables on Page 129, there was a significant decrease in the incidence of diabetes in the rats receiving 1.5 mg/kg dCF, but no apparent effect in the rats receiving 0.5 or 1.0 mg/kg dCF, suggesting a dose-related effect. No drug toxicity was observed at any of the dCF dosages. We are continuing our studies, and will investigate if higher, non-toxic doses of dCF can further decrease the incidence of diabetes, if the protective effect of dCF continues after the drug is discontinued, and if dCF is effective in preventing the progression of diabetes if treatment is begun immediately following the initial onset of this disease.

Dr. James Johnston chats with visiting scientist Masahiro Nishibori

PREVENTION OF DIABETES MELLITUS BY dCF IN BB WISTAR RATS

Exp.	Control	dCF CONCENTRATION (mg/kg/week) 0.5	1.0	1.5
1. No. of Animals	-	6	7	9
No. with Diabetes	-	5	6	3
% with Diabetes	-	83%	86%	33%
2. No. of Animals	9	10	10	10
No. with Diabetes	8	10	8	4
% with Diabetes	89%	100%	80%	40%

Publications

Canvin, M.G., Dalal, B.I., Baragar, F. and Johnston, J.B. Cyclosporin in the treatment of Felty's syndrome. Am. J. Haematol..

Johnston, J.B., Israels, L.G., Goldenberg, G.J., Anhalt, C.D., Pugh, L. Mowat, M.R.A. and Begleiter, A. Glutathione S-transferase, sulfhydryl groups and DNA crosslinking activity with chlorambucil in chronic lymphocytic leukemia. J. Natl. Cancer Inst. 82:776-779, 1990.

Begleiter, A., Jesson, M.I. and Johnston, J.B. Uptake and binding of 3' (3-cyano-4-morpholinyl)-3'-deaminoadriamycin and 3'-(4-morpholinyl)-3'-deaminoadriamycin in L5178Y lymphoblasts in vitro. I Cancer Commun. 2:7-12, 1990.

Begleiter, A. and Leith, M.K. Activity of quinone alkylating agents in quinone resistant cells. Cancer Res. 50:2872-2876, 1990.

Smithgall, T.E., Johnston, J.B., Bustin, M. and Glazer, R.I. Elevated expression of the c-fes-oncogene in adult human myeloid leukemia cells in the absence of gene amplification. J. Natl. Cancer Inst. USA, (in press)(1990).

Weinerman, B., Maroun, J., Stewart, D., Cripps, C. and Johnston, J.B. Sequential methotrexate, 5-fluorouracil and leucovorin metastatic measurable colorectal cancer. Cancer Investigation, Vol. 8, 339-343, 1990.

Abstracts

Begleiter, A., Jesson, M.I. and Johnston, J.B. Uptake and binding of the morpholino analogues of Adriamycin, CMA and MA, in vitro. Proc. Amer. Assoc. Cancer Res. 32:349, 1990.

Israels, L.G., Jesson, M.I., Israels, S., Greenberg, A.H., Begleiter, A. Mowat, M.R.A. and Johnston, J.B. Activity of TGF-β in chronic lymphocytic leukemia (CLL) *in vitro*. Blood, 76(Suppl):283, 1990.

Smithgall, T.E., Johnston, J.B., and Glazer, R.I. Detection of c-*fes* proto-oncogene mRNA in human myeloid leukemia by RNase protection assay. Proc. Am. Assoc. Cancer Res., 31:314, 1990.

Steimack, G.L., Leith, M., Begleiter, A. and Goldenberg, G.J. Increase of gene copy number and expression of glutathione S-transferases (GSTs) in quinone-resistant L5178Y murine leukemia. Clin. Invest. Med. 13:B121, 1990.

Verburg, L., Begleiter, A., Israels L.G. and Johnston, J.B. Mechanisms involved in inhibition of repair of irradiation induced DNA strand breaks (SB) in L5178Y lymphoblasts by 2'-deoxycoformycin (dCF) and deoxyadenosine (dAdo). Proc. Amer. Assoc. Cancer Res. 31:389, 1990.

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Research Reports

STUDIES OF THE MECHANISM OF NATURAL KILLER (NK) DEGRANULATION AND CYTOTOXICITY.

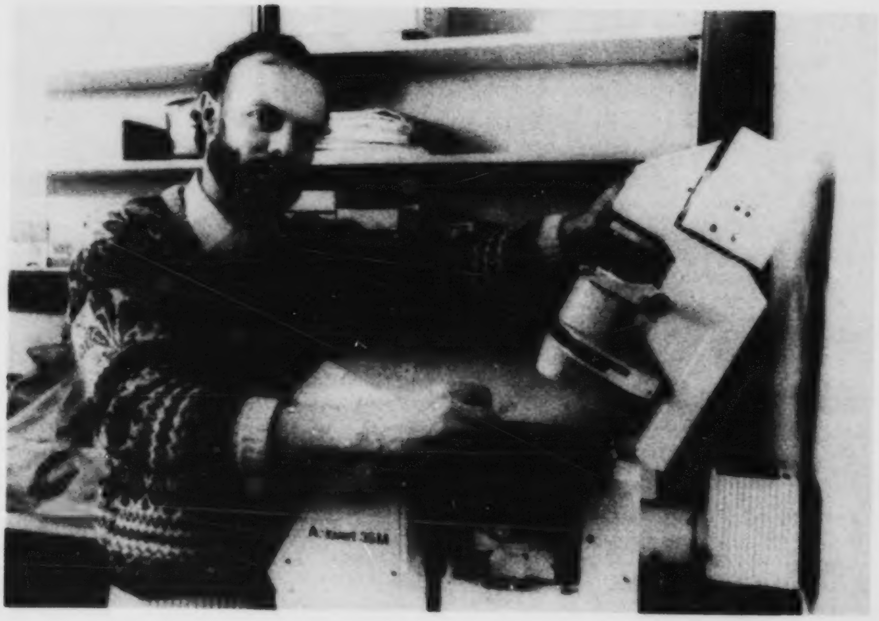
Eric A. Atkinson, Jon M. Gerrard, G. Elske Hildes, and Arnold H. Greenberg

Exocytosis of cytotoxic granule contents towards bound target cells is thought to be of central importance in natural killer (NK) cell-mediated killing. Although cellular cytotoxicity involving degranulation is thought to be calcium-dependent, the biochemical mechanisms that mediate this granule mobilization are unknown. Inositol-1,4,5-tris-phosphate (IP_3), which acts to elevate internal calcium levels, and 1,2-diacylglycerol (DAG), which activates protein kinase C, are potent second messengers that have been shown to synergistically mediate secretion in other cell types. Production of these products of inositol phospholipid metabolism has previously been demonstrated in a rat NK cell line RNK upon exposure to susceptible tumor targets. We, therefore, investigated the role of IP_3 and DAG in NK-mediated cytotoxicity, specifically at the level of degranulation. Pretreatment of RNK cells with neomycin, a drug that interferes with the hydrolysis of inositol phospholipids and thus inhibits the formation of second messengers, inhibited RNK cytotoxicity against a susceptible tumor target and also inhibited RNK production of DAG in response to a similar target. Natural killing exhibited by normal rat nylon wool-nonadherent splenocytes was also inhibited by neomycin. Phorbol-12-myristate,13-acetate (PMA), a phorbol ester that acts like DAG to activate protein kinase C, markedly enhanced lysis of a susceptible target cell by RNK. We evaluated whether modulation of lysis by these drugs was associated with effects on RNK degranulation by assaying the release of a granule-specific serine esterase (BLTE) in response to PMA and the calcium ionophore A23187. These agents synergized to promote the release of BLTE, and the extent of release was dependent on the concentrations of both agents. D_20 and cytochalasin B, which enhance secretion in other cells, both enhanced BLTE release from RNK cells, indicating that we were detecting BLTE released via granule secretion and not due to nonspecific causes such as cell lysis. Our findings lead us to propose that NK cells form IP_3 and DAG in response to susceptible target cells and that a major function of these second messengers is to mediate the exocytosis of cytotoxic granules towards the bound target cells.

INVERSE CORRELATION BETWEEN NATURAL ANTITUMOR ANTIBODIES AND TUMOR SUSCEPTIBILITY IN INDIVIDUAL XID-BEARING MICE.

R.D. Bennet, D.A. Chow

Natural antibodies (NAb), natural killer (NK) cells and activated macrophages have all been implicated in the rejection of threshold syngeneic tumor inocula. Previous analysis of tumor susceptibility in normal versus inbred and F_1 mice bearing the B cell deficiency associated with the xid mutation of CBA/N mice demonstrated an inverse relationship between the tumorigenicity of the RI-28, a radiation-induced leukemia of the CBA/H strain, and the pooled anti-RI-28 serum NAb levels in mice with the same genetic origins. No relationship with tumor susceptibility was seen with NK cell or in vivo activated macrophage cytolysis. Flow-cytometric determination of antitumor serum NAb bled from individual male and female (CBA/N x CBA/J)F_1 mice 1 week prior to the threshold tumor inoculation has revealed extensive heterogeneity within the NAb levels of each sex. A comparative analysis of tumor fate with NAb activity revealed that tumors appeared in only 26.3% of animals with a mean fluorescence channel binding above 60 channels in contrast with 77.3% of animals with lower NAb levels. These data extend to the level of individual hosts



Dr. Jon Gerrard

the support for an inverse relationship between host NAb activity and tumor susceptibility. In addition, subsequent analysis of serum antitumor NAb levels, splenic NK cytolysis and in vivo lymphokine-activated macrophage activity with all three mediators originating from the same individual F_1 mice showed no consistent correlations between these natural resistance activities, arguing for the exclusion of deficiencies in NK cell or macrophage function as the basis for the differential tumor susceptibility in individual F_1 mice.

THE ANTIPROLIFERATIVE POTENCY OF HISTAMINE ANTAGONISTS CORRELATES WITH INHIBITION OF BINDING OF $[^3H]$-HISTAMINE TO NOVEL INTRACELLULAR RECEPTORS (H_{IC}) IN MICROSOMAL AND NUCLEAR FRACTIONS OF RAT LIVER.

L.J. Brandes, J.R. Davie, F. Paraskevas, B. Sukhu, R.P. Bogdanovic, and F.S. LaBella

Previously, we identified in rat liver microsomes, low (µM) affinity histamine receptors (H_{IC}), associated with antiestrogen binding sites (AEBS). N,N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine.HCl (DPPE), a potent AEBS ligand, is a specific H_{IC} antagonist. Through binding H_{IC}, newly-formed intracellular histamine mediates, and DPPE inhibits, human platelet aggregation. We now provide evidence that histamine, mobilized from cytoplasmic stores, is a mediator of the mitogenic response to concanavalin A in mouse spleen cells. DNA synthesis and intracellular histamine levels are decreased over time by the histidine decarboxylase inhibitor, α-fluoromethylhistidine. For DPPE, H_1 and H_2 antagonists, rank order of potency to inhibit $[^3H]$-histamine binding to H_{IC} in rat liver microsomes correlates with antiproliferative potency. DPPE also competes for $[^3H]$-histamine binding at low and high affinity sites in rat liver nuclei (IC_{50} ~ 2 µM). Thus, histamine may mediate growth through two intracellular subtypes of H_{IC}.

STUDY OF THE IN-VIVO ANTIOESTROGEN ACTION OF N, N-DIETHYL-2-[4-(PHENYLMETHYL) PHENOXY]ETHANAMINE.HCl (DPPE), A NOVEL INTRACELLULAR HISTAMINE ANTAGONIST AND ANTIOESTROGEN BINDING SITE LIGAND.

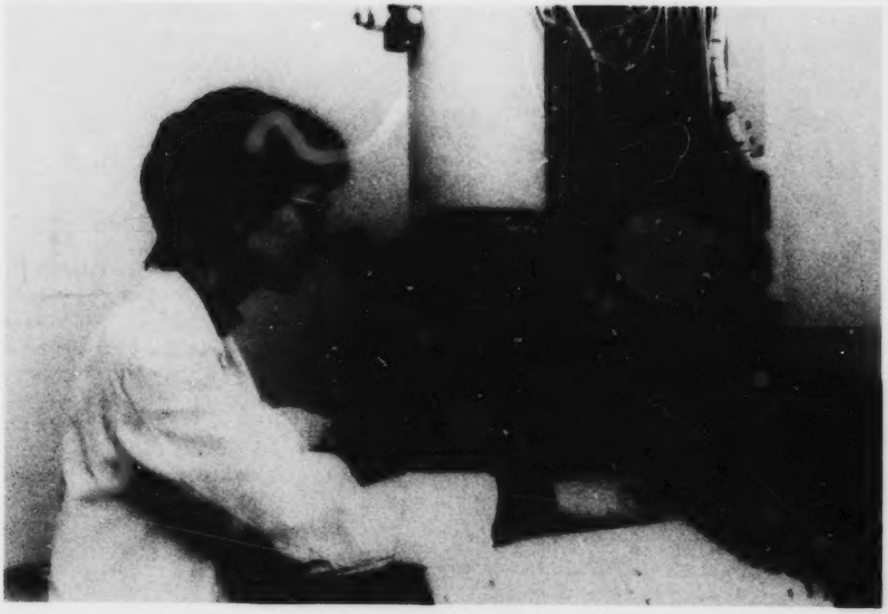
L.J. Brandes and G.R. Hogg

N,N-diethyl-2-[4-(phenylmethyl)phenoxy] ethanamine.HCl (DPPE) binds with high affinity to the antioestrogen binding site (AEBS), but not to the oestrogen receptor. There is an association of AEBS with a novel intracellular histamine receptor (H_{IC}) of micromolar affinity through which histamine acts as a second messenger. An optimal dose of 4 mg DPPE/kg antagonized the uterine growth-stimulating effects of oestradiol in immature oophorectomized rats. Unlike tamoxifen, DPPE alone was not a partial agonist, but decreased uterine size and weight below control values at concentrations between 0.1 and 75 mg/kg. DPPE also antagonized oestradiol-stimulated uterine growth at 72 h; the inhibition observed was not significantly different from that seen with tamoxifen. Oestradiol-treated animals receiving the combination of DPPE (4 mg/kg) + low dose tamoxifen (0.04 mg/kg) for 72 h had significantly smaller uteri than did those receiving the same dose of DPPE or tamoxifen alone. Histologically, either DPPE or tamoxifen antagonized oestradiol stimulation of eosinophil migration and glandular epithelial proliferation; the latter inhibition was significantly greater for DPPE + tamoxifen (0.04 mg/kg) than for the same dose of DPPE or tamoxifen alone. Unlike tamoxifen, DPPE did not antagonize oestradiol stimulation of luminal epithelial proliferation, but in the presence of oestradiol, DPPE significantly decreased tamoxifen (0.65 mg/kg)-induced hypertrophy of the luminal epithelium. Based on these findings, we suggest that binding to the AEBS/intracellular histamine receptor is important to the action of antioestrogens.

HISTAMINE AS AN INTRACELLULAR MESSENGER

Lorne J. Brandes, Frank S. LaBella, Gary B. Glavin, Frixos Paraskevas, Satya P. Saxena, Archibald McNicol and Jon M. Gerrard.

Through the synthesis of N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine.HCl (DPPE), a potent ligand for the microsomal antiestrogen binding site (AEBS) to which tamoxifen (TAM) binds, we have identified the existence of a novel low (mm) affinity intracellular histamine receptor (designated H_{IC}), which may be associated with AEBS. As a result of binding to H_{IC}, histamine (a) mediates platelet aggregation, and (b) as postulated by Kahlson and Rosengren twenty-five years ago,



Dr. Sara Israels at the electron microscope

is implicated in cell proliferation and other important physiological processes.

With our discovery of H_{IC} and its role in mediating agonist-induced platelet aggregation, histamine now joins a small group of other chemicals which qualify as true intracellular messengers; cAMP, cGMP, calcium, inositol triphosphate and diacylglycerol. In addition, a strong case has been made for polyamines as intracellular messengers; other amines ultimately may join in this select list. Further studies are underway to define such a role for histamine in growth and in cell systems other than platelets. Ultimate acceptance of the second messenger histamine hypothesis also will depend upon independent confirmation in other laboratories, and the clarification of interactions of intracellular histamine with other second messenger and signal transduction pathways. Finally, interaction at an intracellular histamine site and triphenylethylene-derivative antiestrogens now must be considered in the overall pharmacological profile of these agents.

DOES INTRACELLULAR HISTAMINE MEDIATE MAST CELL HISTAMINE RELEASE?

Lorne J. Brandes, Balram Sukhu and R. Patricia Bogdanovic

Previously, we demonstrated that through binding a novel intracellular receptor of mM affinity (H_{IC}), histamine mediates, and the H_{Ic} antagonist N,N-diethyl-2-[4(phenylmethyl) phenoxy]ethanamine.HCl (DPPE) inhibits, platelet aggregation and serotonin granule secretion; the latter response is dependent upon the same processes that mediate histamine release from mast cell granules. We now show that, as for platelet serotonin release, DPPE blocks concanavalin A-stimulated mast cell histamine release with a potency (IC_{50} = 30 μM) greater than the H_1-antagonist, pyrilamine (IC_{50} = 150 μM) or the H_2-antagonist cimetidine (IC_{50} = 5 μM), correlating with rank order of potency to inhibit ^{3}H-histamine binding in rat brain membranes and liver microsomes. We postulate that histamine release from mast cells is mediated at H_{IC} by second messenger intracellular histamine. However, unlike platelets, mast cells do not appear to rely on newly synthesized histamine. Rather, as for calcium, histamine may be mobilized from bound stores to mediate histamine secretion.

RNK CYTOTOXIC GRANULE EXTRACT: DIFFERENTIAL SENSITIVITY OF AN NK-SENSITIVE AND AN NK-RESISTANT MURINE LYMPHOMA

Donna A. Chow

Natural killer (NK) cell resistant tumors exist despite their ability to bind from cells from the effector population. Tumor sensitivity to NK activity was therefore examined at the level of susceptibility to cytolysin-containing NK cell cytotoxic granule extracts. The NK-sensitive SL2-5 murine lymphoma was markedly more susceptible than the NK-resistant L5178Y-F9 to solubilized granule preparations from the rat NK tumor cell line RNK-16 and this corresponded directly with tumor-sensitivity to hypotonic lysis and inversely with their production of granule extract-inhibitory supernates. L5178Y-F9 cells exposed to 0.25 M MaCl produced more inhibitory supernate and were more sensitive as extract targets. The inhibitory material is stable at room temperature and upon freezing and the majority of the activity can be concentrated on a UM10 Diaflo filter, suggesting a molecular weight of 10 kd or greater. Thus tumor supernates clearly inhibited extract cytolysis and the inhibition appears to be due to a high molecular weight material released preferentially into the supernate by the NK-resistant L5178Y-F9. This material acts as an inhibitor of cytolysin binding and appears to be released in greater quantities in high NaCl-containing media.

Dr. Nasreen Khalil

RNK GRANULE EXTRACT CYTOLYSIS: INCREASED TUMOR SUSCEPTIBILITY AND RELEASE OF PROTEOCHONDROITIN SULPHATE INHIBITOR IN HIGH NaCl.

Donna A. Chow

The insensitivity of the natural killer (NK)-resistant L5178Y-F9 murine T-cell lymphoma to granule extracts from a rat NK leukemia could be preferentially reversed in increased NaCl (0.25 M) compared with the NK- and granule extract-sensitive SL2-5. The high salt effect predominated in the binding rather than the lytic phase of the extract reaction similar to the activity of extract inhibitory supernates preferentially produced from L5178Y-F9 cells. Exposure of the L5178Y-F9 to 0.25 M NaCl was associated with an increased production of inhibitory supernate and an increased sensitivity of the cell as an extract target. Pretreatment of inhibitor-containing supernatant or inhibitor-producing L5178Y cells with pronase or chondroitinase AC reduced the inhibitory activity of the resultant supernates, and L5178Y-F9 supernates treated with anti-chondroitin sulphate AC antibodies exhibited reduced inhibitory activity. These observations and the previously reported molecular weight heterogeneity and protease sensitivity of the inhibitor argue that chondrointin sulphate AC-containing proteoglycans released from the tumor cell surface may inhibit cytolysin activity, contributing to the preferential resistance of the L5178Y-F9 to rat NK granule extract cytolysis.

IDENTIFICATION OF A PLATELET DENSE GRANULE MEMBRANE PROTEIN THAT IS DEFICIENT IN A PATIENT WITH THE HERMANSKY-PUKLAK SYNDROME

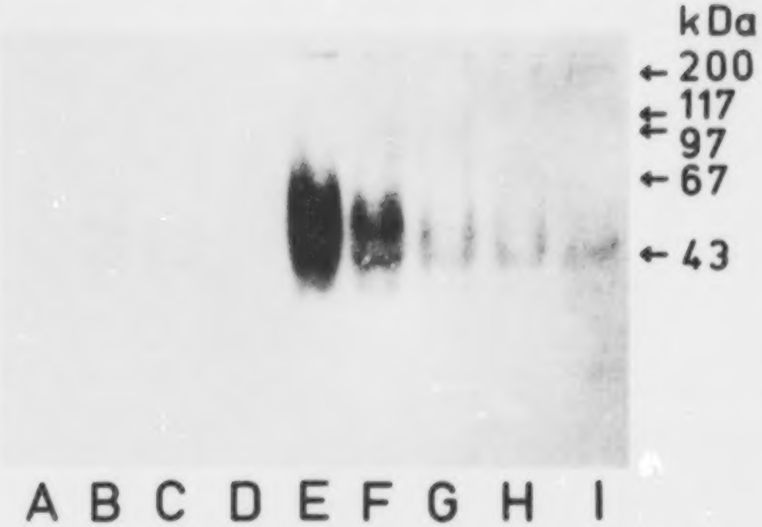
J.M. Gerrard, D. Lint, P.J. Sims, T. Wiedmer, R.D. Fugate, E. McMillan, C. Robertson and S.J. Israels

Monoclonal antibodies were raised after injecting mice with isolated human dense granules. Several of these monoclonals were found to recognize a 40-kD dense granule membrane protein. Western blot and immunofluorescent analysis confirmed the dense-granule specificity. After thrombin activation, the protein was found in patches on the external platelet membrane. By Western blot and slot blot analysis, the protein was found to be markedly deficient in a patient with the Hermansky-Pudlak syndrome. Studies of neutrophils and endothelial cells show the presence of immunologically related granule-membrane protein(s). Western blots using four anti-synaptophysin antibodies and three antibodies to the platelet 40-kD protein suggest that the protein may share some homology with, but is not identical to, the synaptosomal membrane protein synaptophysin.

STUDIES IN PATIENTS WITH BLEEDING DISORDERS SHOW THAT PLATELET-VESSEL INTERACTION IS IMPORTANT FOR THROMBOXANE FORMATION IN BLEEDING TIME WOUNDS.

Jon M. Gerrard, Sandra Singhroy, Elena Duta, Barbara Nosek-Cenkowska, Sara J. Israels, Esther D. Israels

The production of thromboxane B_2, the primary metabolite of thromboxane A_2, and 6-keto prostaglandin F_{1a} the primary metabolite of prostacyclin, were measured in response to a standardized vascular injury, the bleeding time, in patients with von Willebrand's disease and in patients with platelet function defects. Compared to controls, thromboxane B_2, levels in bleeding time blood were significantly lower in subjects with von Willebrand's disease. In patients with platelet function defects associated with a deficient response to thromboxane A_2, thromboxane B_2 production in bleeding time blood was similar to controls. In subjects with other platelet function defects, thromboxane production was significantly lower than normal. 6-keto PGF_{1a} reduction in bleeding time blood was not significantly different in patients compared to controls. The results suggest that bleeding time thromboxane production is influenced by the extent of platelet-vessel interaction.



Western blot showing serial dilutions of whole platelet homogenate from a patient with the Hermansky-Pudlak (HP) syndrome (lanes A through D) and a normal control (lanes E through I) showing a deficiency in granulophysin in the patient with the HP syndrome.

THE PAVLOVIAN CONDITIONING OF INTERLEUKIN-1 (IL-1)-INDUCED GLUCOCORTICOID SECRETION

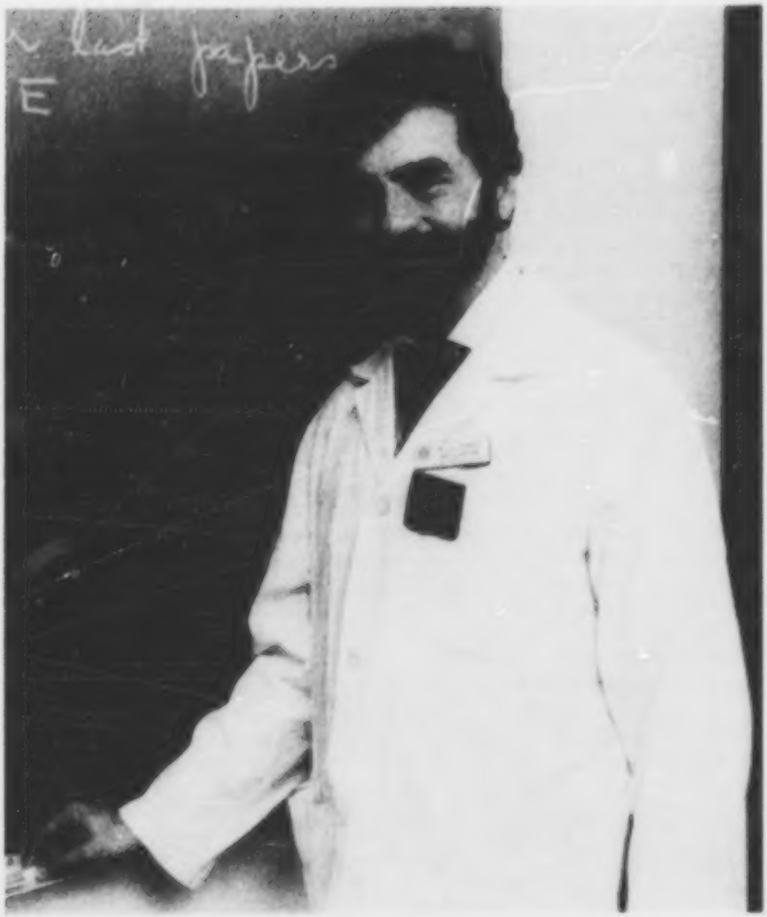
Arnold H. Greenberg, Loren Janz, Timothy A.G. Osachuk, Jason Falk, Jorden Labinsky and Dennis G. Dyck

Recombinant IL-1ß, which is capable of stimulating the pituitary adrenal axis to secrete corticosterone, was paired with environmental cues in either a taste aversion or odor conditioning procedure. Among mice receiving paired delivery of cues and IL-1, subsequent reexposure to cues only elicited corticosterone production. This response was significantly greater than in animals that were conditioned but not reexposed to the cues, or were exposed to the cues alone. These results indicate that the normal pathway for IL-1 activation of adrenal cortical secretion can be conditioned to environmental stimuli and support a mechanistic model of conditioned immunosuppression.

INHIBITION OF INTRAVASCULAR PLATELET AGGREGATION BY ENDOTHELIUM-DERIVED RELAXING FACTOR: REVERSAL BY RED BLOOD CELLS.

Donald A. Houston, Pauline Robinson and Jon M. Gerrard

Studies were performed to determine whether endothelium-derived relaxing factor (EDRF) can inhibit platelet aggregation within the vascular lumen, and if so, whether the inhibition persists in the presence of red blood cells (RBCs). Canine femoral arteries mounted in an organ bath were



Dr. Lorne Brandes

perfused with physiological saline solution to which acetylsalicylic acid was added to block prostacycline formation. During contraction with phenylephrine, addition of acetylcholine to the perfusing solution to evoke EDRF release relaxed the vessel wall. Washed human platelets labeled with ^{14}C-5-hydroxytryptamine were added to the perfusing solution, and activated by thrombin infused via a branch vessel. The perfusate was collected downstream and centrifuged; the fraction of ^{14}C-5-hydroxytryptamine appearing in the supernatant reflected the degree of platelet activation. Stimulation of EDRF release with acetylcholine inhibited ^{14}C-5-hydroxytryptamine release. Hemoglobin (Hb)(10^{5} mol/L) blocked vascular relaxation and platelet inhibition. RBCs at a hematocrit to 10% (treated with echothiophate to block erythrocyte cholinesterase) did not prevent relaxation but reversed the platelet inhibition. Lower hematocrits did not completely block the inhibition. Thus, erythrocyte Hb may modulate the inhibition of intraluminal platelet aggregation by EDRF.

DEFICIENT COLLAGEN-INDUCED ACTIVATION IN THE NEWBORN PLATELET

Sara J. Israels, Michele Daniels, and Eileen M. McMillan

We have investigated the imparied secretion response of neonatal platelets. We compared the response of washed neonatal and adult platelets to thrombin and collagen, and to specific activators of calcium flux (inositol trisphosphate) and protein kinase C actiavtion (oleoyl-acetyl glycerol). Neonatal platelets show no impairment of aggregation, secretion of [^{14}C]serotonin or phosphorylation of specific intracellular proteins in response to thrombin, inositol trisphosphate, or oleoyl-acetyl glycerol. However, neonatal platelets have a markedly decreased response to collagen. To further evaluate this deficient response, we examined specific aspects of the collagen activation pathway. Collagen-platelet interaction as measured by adhesion of platelets to collagen-coated dishes showed no difference in adhesion of neonatal platelets compared to adult controls (20.1 ± 11.6 versus 18.6 ± 9.3%). The presence of GPIa/IIa, a Mg^{2+}-dependent collagen receptor, was evaluated by flow cytometric analysis of binding of fluorescein-tagged monoclonal antibody, 6F1 (directed against GPIa/IIa). There was no difference either in the percent of platelets that bound antibody (80 versus 81%) or in the mean fluorescence intensity of the adult and neonatal samples. Phosphoinositide hydrolysis was decreased in neonatal platelets in response to collagen but normal in response to thrombin. Neonatal platelets released more arachidonic acid than adult platelets in response to thrombin (29.5 ± 3.2 versus 19.6 ± 1.8%) but less than adult platelets in response to 10μg/ml collagen (3.2 ± 1.1 versus 9.3 ± 3.0%). Thromoxane B_2 production was also decreased in response to collagen (52.7 ± 12.6 versus 101.4 ± 18.7 ng/ml). These results suggest that the deficient collagen response in neonatal platelets may lie in transduction of the collagen signal to phospholipases A_2 and C.

PLATELET STORAGE POOL DEFICIENCY: DIAGNOSIS IN PATIENTS WITH PROLONGED BLEEDING TIMES AND NORMAL PLATELET AGGREGATION.

S.J. Israels, A. McNicol, C. Robertson and J.M. Gerrard

We evaluated 46 patients with prolonged bleeding times, and no demonstrable abnormalities of either von Willebrand factor or platelet aggregation, for possible deficiency of platelet storage pool. Studies of ATP release from thrombin-stimulated platelets and enumeration of dense granules in platelet whole mounts were performed in these patients. Seventeen patients (35%) had both decreased ATP release and decreased numbers of dense granules, suggesting the presence of a storage pool defect. Thus, storage pool deficiency may be present in the absence of the classical aggregation abnormalities. Evidence of storage pool deficiency should be considered in all patients with an isolated unexplained prolongation of the bleeding time. The methods used in this study are readily applicable to most clinical laboratories.

Dr. Frixos Paraskevas and Technician, Margaret Wilcock, at the EPICS C cytofluorometer

IDIOPATHIC PULMONARY FIBROSIS: NEW INSIGHTS INTO PATHOGENESIS AND THERAPY

N. Khalil

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology, characterized by relentlessly progressing pulmonary fibrosis and a markedly reduced life span. The pathogenesis of IPF is unknown, but recent evidence indicates that peptide growth factors such as transforming growth factor-beta (TGF-β) may be pathogenic to the inflammation and fibrosis seen in this disease. Therapy for IPF remains unsuccessful, but it is possible that early detection and treatment with immunosuppressive drugs prior to the onset of late stage disease may prolong life expectancy.

GROWTH FACTOR-INITIATED PROLIFERATION OF MOUSE EMBRYONIC FIBROBLASTS INDUCES CYTOTOXICITY BY NATURAL KILLER CELLS AND BY A NON-CYTOLYSIN CYTOTOXIN IN NATURAL KILLER GRANULES.

N.I. Khalil, S.C. Battistuzzi, R.P. Kraut, L.C. Schwarz and A.H. Greenberg

NK cells preferentially kill normal embryonic fibroblasts. Because embryonic cells are growth factor responsive and maintain high proliferative rates, we examined the requirement for growth factor-initiated proliferation for NK susceptibility. Murine embryonic fibroblasts made quiescent in defined medium lacking growth factors were relatively resistant to NK cytolysis. However, reinitiation of proliferation with basic fibroblast growth factor (bFGF) or epidermal growth factor enhanced lysis in a dose-dependent fashion. TGF-β, which blocked cell division, did not enhance cytotoxicity. Additionally, growth inhibition by prolonged incubation at confluence suppressed lysis. The enhanced NK cytotoxicity of bFGF-stimulated fibroblasts was caused by a post-binding event because no difference in cold target inhibition could be demonstrated with bFGF-treated cells. NK cytotoxicity has largely been attributed to the action of cytotoxins released from cytoplasmic granules. In a ^{51}Cr release assay, bFGF-treated fibroblasts were insensitive to NK granules isolated from the RNK large granular lymphocyte leukemia. However, these same cells exhibited marked sensitivity to lysis in an 18-h adhesion assay normally utilized to detect TNF-α. With the use of this assay, a dose-dependent increase in sensitivity of bFGF-treated fibroblasts was observed, whereas quiescent fibroblasts were resistant to the action of isolated NK granules. Granule cytotoxicity was not caused by cytolysin/perforin because inactivation of granule hemolytic activity with $CaCl_2$ did not affect fibroblast killing, and bFGF-treated cells were insensitive to purified cytolysin/perforin. This suggested that another granule associated cytotoxin was responsible for enhanced NK sensitivity of actively proliferating fibroblasts.

ALVEOLAR MACROPHAGES FROM BLEOMYCIN-INDUCED PULMONARY INFLAMMATION SYNTHESIZE AND SECRETE TRANSFORMING GROWTH FACTOR-BETA (TGF-β)

N. Khalil, O. Bereznay and A.H. Greenberg

A rat model of bleomycin-induced pulmonary fibrosis (BPF) and inflammation was used to examine the relationship between collagen synthesis and TGF-β production and distribution. TGF-β was elevated 2 hours after intratracheal bleomycin and peaked at 7 days after bleomycin administration. Peak TGF-β levels preceded maximal collagen synthesis at 14 days. At the time of peak TGF-β levels immunohistochemical staining localized TGF-β intracellularly in clusters of macrophages found in the alveoli. At times of peak collagen synthesis TGF-β was localized to the extracellular matrix (ECM).

Although alveolar macrophages (AM) were observed to contain large quantities of TGF-β intracellularly, to demonstrate that AM also secrete TGF-β we obtained AM from bleomycin treated rats and normal saline controls 7 days after treatment by bronchoalveolar lavage. Conditioned

Dr. Brent Schacter and technician, Mukhtiar Singh

medium (CM) from overnight cultures of AM obtained from control treated animals showed no TGF-β activity in a CCL-64 mink epithelial bioassay. However, AM from bleomycin-treated animals secreted 2.1 pg • 0.37 of active TGF-β/10^6 macrophages. Acidification of the CM resulted in activation of latent TGF- β and a total of 3.96 pg • 0.82 of TGF-β/10^6 macrophages was detected

Corticosteroids inhibit mononuclear cell influx into injured tissue. If alveolar macrophages were a major source of TGF-β at 7 days after bleomycin then inhibition of macrophage influx into injured lungs would diminish total lung TGF-β production. Using immunosuppressive doses of methylprednisone-acetate we were able to demonstrate that 7 days after bleomycin administration, total lung TGF-β levels were 9% of animals treated with bleomycin but no methylprednisone.

These findings indicate that alveolar macrophages synthesize TGF-β and secrete it in the active and latent forms during bleomycin-induced inflammation. Furthermore, methyl-prednisone-acetate can abrogate the peak of TGF-β production seen 7 days after bleomycin administration.

TRANSFORMING GROWTH FACTOR-b PRODUCTION AND IMMUNOHISTOCHEMICAL LOCALIZATION DURING BLEOMYCIN-INDUCED PULMONARY INFLAMMATION.

N. Khalil, O. Bereznay, M.B. Sporn and A.H. Greenberg

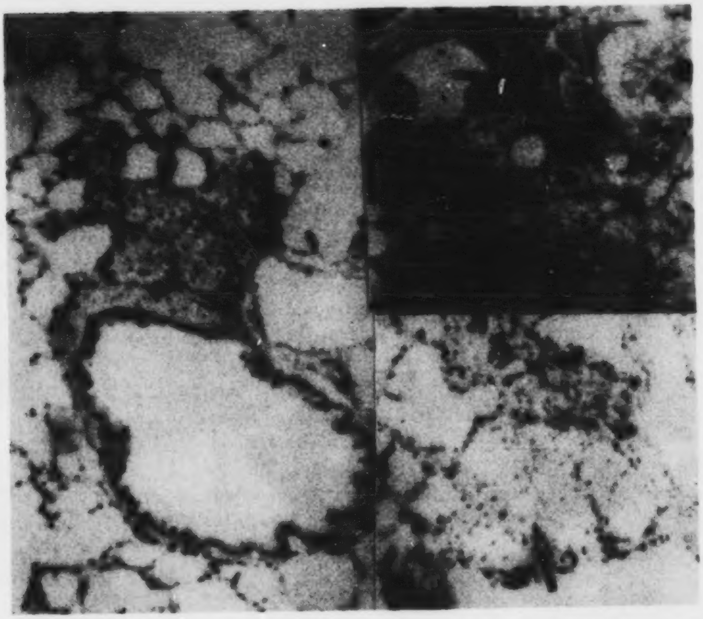
Transforming growth factor-b (TGF-β), a 25 kD homo-dimer and heterodimer is a multifunctional regulator of cell growth and differentiation. A number of previously described TGF-β functions suggest a role in tissue repair. TGF-β is a chemoattractant for monocytes and fibroblasts. TGF-β induces monocytes to secrete IL-1, a potent mitogen for fibroblasts, and by itself can stimulate proliferation of immature fibroblasts. TGF-β enhances synthesis of collagen, fibronectin and proteoglycans. In vivo TGF-β stimulates granulation tissue, angiogenesis, and increased collagen synthesis. The pathogenesis of chronic pulmonary fibrosis is not well understood but based on animal models, the fibrotic response is preceded by an influx of inflammatory cells. Because of the well described effects of TGF-β oninflammatory cells and connective tissue, we examined the relationship between collagen synthesis and TGF-β production and distribution in a rat model of bleomycin-induced inflammation and fibrosis.

Total lung TGF-β was elevated 2 h after intratracheal bleomycin administration and peaked at 7 days. TGF-β gradually declined with persistent levels of production up to 28 days. Peak TGF-β levels preceded the maximum collagen and non-collagen protein synthesis at 14 days by fibroblasts isolated from lung explants of belomcyin-treated rats. Immunohistochemical staining localized TGF-β initially in the cytoplasm of bronchiolar epithelium cells and the subepithelial extracellular matrix. Peak lung TGF-β levels at 7 days coincided with intense TGF-β staining of scattered alveolar macrophages while subsequently TGF-β producing macrophages were found in organized clusters. After 7 days TGF-β was primarily associated with extracellular matrix in regions of increased cellularity and tissue repair, and this staining pattern coincided with the maximum fibroblast collagen synthesis. Staining in all tissues could be blocked with TGF-β peptide 1-30, or by preabsorbing antiserum with insolubilized TGF-β.. These temporal and spatial relationships between collagen production and TGF-β production by macrophages suggest a role for TGF-β in the pathogenesis of the pulmonary fibrosis produced by bleomycin.

TGF-β IN PULMONARY FIBROSIS.

N. Khalil and A.H. Greenberg

Pulmonary fibrosis is an irreversible accumulation of connective tissue in the interstitium of the lung. The pathogenesis of pulmonary fibrosis is not well understood. However, research on animal models and studies of human lung disease suggest the initiating events may be a combination of pulmonary injury and the recruitment of inflam-



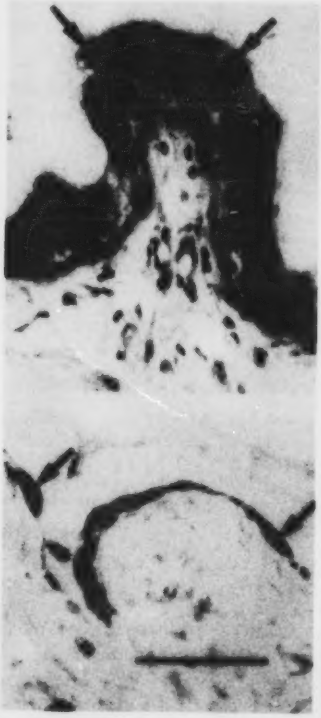
Immunohistochemical localization of TGF-β to alveolar macrophages after bleomycin treatment of the rat. (A) TGF- β localized the alveolar macrophages which were organized in clusters seven days after bleomycin (arrow). An avidin-biotin alkaline phosphatase staining appears as dark grey (bar, 100 µm). (B) Higher power magnification of macrophages shows clusters are adjacent to mild interstitial hypercellularity (bar, 50 µm). (c) Absence of macrophage staining (arrow) using normal rabbit IgG in place of LC antibody.

matory cells, mainly macrophages. A number of well characterized cytokines, including TGF-β, have either been found in the injured lung or have been produced by the inflammatory cells removed from the lung. In an animal model of pulmonary fibrosis, TGF-β production is increased prior to collagen synthesis and is primarily produced by alveolar macrophages. In advanced idiopathic pulmonary fibrosis, a human fibrotic lung disease, extensive TGF-β deposition can be detected by immunohistochemical staining localized primarily in epithelial cells in areas of lung regeneration and remodelling. This suggests that the pathogenesis of the progressive fibrosis characteristic of this lung disease may be an abberant repair process.

INCREASED PRODUCTION AND IMMUNOHISTOCHEMICAL LOCALIZATION OF TRANSFORMING GROWTH FACTOR-BETA (TGF-β) IN IDIOPATHIC PULMONARY FIBROSIS.

N. Khalil, R. O'Connor, H. Unruh, P. Warren, A. Kemp, O. Bereznay, K. Flanders and A.H. Greenberg

Transforming growth factor-beta (TGF-β) can regulate cell growth and differentiation, as well as production of extracellular matrix proteins. Elevated production of TGF-β has been associated with human and rodent chronic inflammatory and fibrotic diseases. Using immunohistochemical staining, we have examined lung sections of patients with advanced idiopathic pulmonary fibrosis (IPF), a disease characterized by chronic inflammation and fibrosis and demonstrated a marked and consistent increase in TGF-β production in epithelial cells and macrophages when compared to patients with non-specific inflammation and those with no inflammation or fibrosis. In patients with advanced IPF, intracellular staining with anti-LC (1-30) TGF-β antibody was seen prominently in bronchiolar epithelial cells. In addition, epithelial cells of honeycomb cysts and hyperplastic type II pneumocytes stained intensely. Anti-CC (1-30) TGF-β antibody, which reacts with extracellular TGF-β, was localized in the lamina propria of bronchioles and in subepithelial regions of honeycomb cysts in areas of dense fibroconnective tissue deposition. The close association of subepithelial TGF-β to the intracellular form in advanced IPF suggests that TGF-β was produced and secreted primarily by epithelial cells. Because of the well known effects of TGF-β on extracellular matrix formation and on epithelial cell differentiation, the increased production of TGF-β in advanced IPF may be pathogenic to the pulmonary fibrotic and regenerative responses seen in this disease.



Immunohistochemical localization of TGF-β to epithelial cells in idiopathic pulmonary fibrosis. Top: Anti-TGF-b antibody staining using avidin-biotin peroxidase localized to the bronchiolar epithelium (arrows) and appears as black (bar, 50 μM). Bottom: Hyperplastic type II pneumocytes stained intensely with anti-TGF-β antibody.

THE INFLUENCE OF CALCIUM, SODIUM, AND THE Na^+/Ca^{++} ANTIPORT ON SUSCEPTIBILITY TO CYTOLYSIN/ PERFORIN-MEDIATED CYTOLYSIS

Ricky P. Kraut, Deepak Bose, Edward J. Cragoe Jr., and Arnold H. Greenberg

In NK cell-mediated cytolysis, the degranulation of the NK cell, and the binding and polymerization of its effector molecule cytolysin/perforin, are Ca^{++}-dependent. To determine if increases in the target cell free intracellular Ca^{++} concentration ($[Ca^{++}]_i$) are also important for cytotoxicity, we examined the effects of Ca^{++} substitutes, promotors of Ca^{++} influx, and inhibitors of Ca^{++} efflux on the cytolysis mediated by purified cytolysin. Ca^{++} promoted cytolysin-mediated cytolysis but could also inactivate cytolysin on pre-incubation in the absence of target cells. Ba^{++} and Sr^{++} could not alone promote cytolysin-mediated cytolysis but did enhance Ca^{++}-driven cytolysis. Since pre-incubation with Ba^{++} and Sr^{++} did notinactivate cytolysin, one interpretation which these results suggested was that neither Ba^{++} nor Sr^{++} were involved in cytolysin polymerization and pore formation, but could act intracellularly as Ca^{++} analogues once pore formation had occurred. The synergistic interaction of cytolysin and the Ca^{++} ionophore A23187 further supported a role for increased $[Ca^{++}]_i$ in cytolysis. Inhibitors of Na^+/Ca^{++} exchange, namely low Na^+ medium, ouabain, and the amiloride analogues 2',4'-dimethylbenzamil, 5-(N-4-chlorobenzyl)-2',4'dimethylbenzamil, and a-phenylbenzamil all markedly enhanced cytolysin-mediated cytolysis. These results support the hypothesis that the Ca^{++} dependency of NK cell- and cytolysin-mediated cytolysis is related to increases in target cell $[Ca^{++}]_i$. Furthermore, they indicate that Na^+/Ca^{++} exchange is an important counterlytic mechanism.

REGULATION OF ANTIBODY SYNTHESIS

F. Paraskevas

Interleukins are growth and differntiation factors which orchestrate all immune and inflammatory responses. T cells constitute one of the main sources for these factors but depending on the nature of antigenic stimulation T cells produce different kinds of interleukins. The nature of the signals which dictate this differential interleukin secretion is unknown. Evidence from our laboratory suggests that a soluble "complex" composed of Ig and antigen formed through the mediation of a T cell factor may regulate interleukin gene expression. Different Ig isotypes participate in the formation of these "complexes". The Ig isotype of the complexes dictates the isotype of the antibody produced. We have shown that exposure of T cells in vitro to these complexes results in enhanced mRNA synthesis for certain interleukins

Our hypothesis, based on preliminary evidence, suggests that IgG2a containing complexes will enhance transcription of the IFN-γ and (probably) IL-2 genes while the IgA complexes will enhance expression of IL-4 and IL-5 genes.

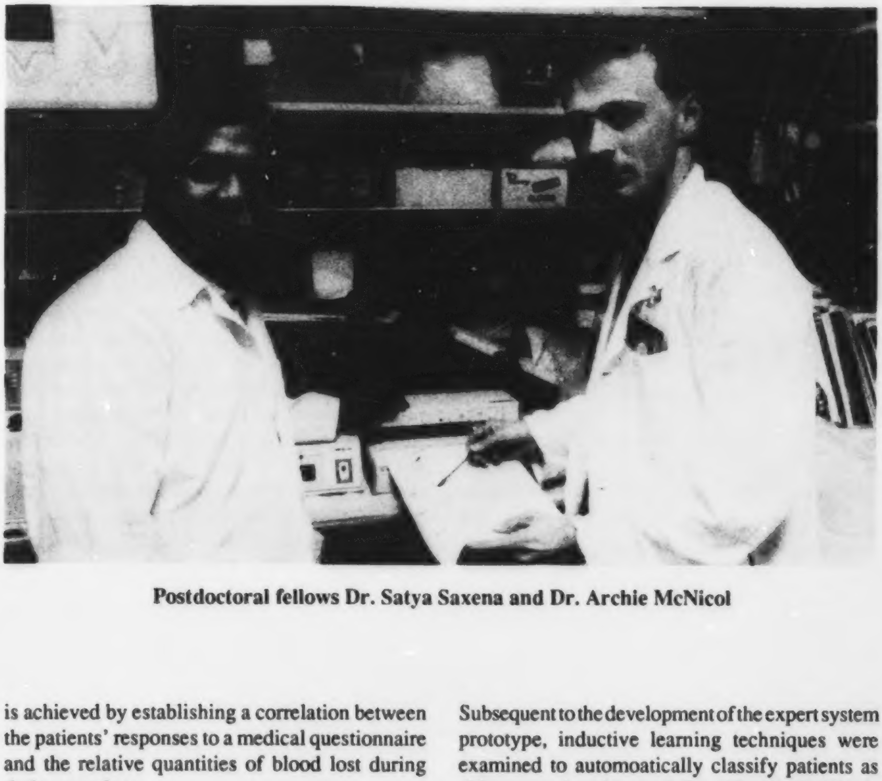
Finally our work explores the role of various combinations of "lymphokines" in the regulation of the secretion of various isotypes. For example, while TGF-β blocks antibody synthesis of all isotypes, addition of certain lymphokines preferentially gives rise to IgM production, or both IgM and IgG production.

In summary, the research program explores an area of intense investigations aimed at the clarification of the regulation of the antibody response.

EXPERT SYSTEM APPROACH TO ASSESSMENTS OF BLEEDING PREDISPOSITIONS IN TONSILLECTOMY/ADENOIDECTOMY PATIENTS.

Nicolino J. Pizzi and Jon M. Gerrard

The purpose of this expert system is to assess a predisposition to bleeding in a patient undergoing a tonsillectomy and/or adenoidectomy, as many occur with patients who have certain blood conditions such as hemophilia, von Willebrand's disease, and platelet function defects. This objective



Postdoctoral fellows Dr. Satya Saxena and Dr. Archie McNicol

is achieved by establishing a correlation between the patients' responses to a medical questionnaire and the relative quantities of blood lost during their operations.

Three major modules constitute the system: the automated questionnaire to be completed by the patient, the expert system proper, and the patient database. The questionnaire is divided into fourteen sections on topics such as the occurrence of bruises and positive familial history. The expert system takes the responses to the questionnarie and determines risk categories for patients undergoing the operations. The patient database contains the patients' questionnaire responses, personal data and the risk assessments generated by the expert system.

Subsequent to the development of the expert system prototype, inductive learning techniques were examined to automoatically classify patients as either normal or abnormal. Specifically, Quinlan's ID3 induction algorithm was used whereby a training set of patient data generates a classification tree whose leaf nodes correspond to the classification outcomes.

This paper presents the architecture of the hematology expert system, identifies some problems encountered during the knowledge engineering process and presents some statistical data pertaining to the accuracy of its risk assessments. It also offers a comparative review of the expert system and inductive learning methodologies.

LONG-TERM CULTURES OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES WITH RECOMBINANT HUMAN INTERLEUKIN-2 GENERATE A POPULATION OF VIRTUALLY PURE CD3$^+$, CD16$^-$ CD56$^-$ LARGE GRANULAR LYMPHOCYTE LAK CELLS.

E. Roussel, J.M. Gerrard, A.H. Greenberg

It has been reported that lymphocytes from peripheral blood (PBL) cultured with interleukin-2 (IL-2) produce predominantly CD16$^-$ lymphokine-activated killer (LAK) cells. We developed a two-step method to generate LAK cells from human PBL in long-term cultures (10-12 days) with recombinant human IL-2 (rhIL-2) and characterized the evolving LAK cell population by testing its phenotype and cytotoxic activity as a function of time. The starting PBL displayed some natural killer (NK) cytotoxicity but no LAK activity. At day 6, the cells were a mixed population of about 80% CD3$^-$ and 6% CD16$^-$ cells. Little proliferation was evident but strong LAK activity was detected. After 10-12 days, major cell expansion had occurred and they were essentially a pure (>90%) CD3$^+$ CD16$^-$ CD56$^-$ cell population large granular lymphocyte (LGL) by morphology that displayed strong non-MHC-restricted killing activity (>200 lytic units). Over the same period of time, the CD16$^-$ cells had almost completely regressed in these cultures. This preferential induction of CD$^+$ LAK cells was not an effect of IL-2 concentration as 10 U/ml was as effective as 500 U/ml. Further characterization revealed a major population of CD4$^+$ (60%) and CD8$^+$ (30%) with a smaller fraction (<9%) of ld $^+$ cells. These results indicate that a virtually pure CD3$^+$ LAK cells population was produced with long-term cultures of lymphocytes from pheripheral blood in rhIL-2 in which active proliferation of the CD3$^+$ but not CD16$^+$ cells occurred.

A ROLE FOR INTRACELLULAR HISTAMINE IN COLLAGEN-INDUCED PLATELET AGGREGATION.

S.P. Saxena, A. McNicol, L.J. Brandes, A.B. Becker and J.M. Gerrard

We previously demonstrated that newly-formed intracellular histamine mediates platelet aggregation in response to phorbol-12-myristate-13-acetate (PMA). We now report further investigations of the role of histamine during physiological activation of platelets by collagen. Platelets stirred with collagen produced histamine; the rise in histamine precedes the onset of aggregation. The dose response for collagen stimulation of histamine synthesis and platelet aggregation is similar. Inhibitors of histidine decarboxylase (HDC) block both aggregation and histamine synthesis in parallel. Histamine production is not dependent on aggregation; both the intracellular histamine receptor antagonist, N,N-diethyl-20[4-(phenylmethyl) phenoxy]ethanamine.HCl (DPPE), and the cyclooxygenase inhibitors, aspirin and indomethacin, inhibit collagen-induced aggregation but not histamine synthesis. DPPE also inhibits collagen-induced serotonin secretion and thromboxane production. The effects of DPPE and HDC inhibitors are significantly reversed by the addition of histamine (0.1 to 10 mmol/L) to saponin-permeabilized platelets, though histamine alone has no pro-aggregatory effects. The results suggest that newly synthesized intracellular histamine has a role in collagen-induced platelet activation and that it may act to promote the generation of thromboxane and the secretion responses of platelet granules.

STRUCTURAL STUDIES ON BOVINE SPLEEN HEME OXYGENASE: IMMUNOLOGICAL AND STRUCTURAL DIVERSITY AMONG MAMMALIAN HEME OXYGENASE ENZYMES.

B.S. Schacter, V. Cripps, R.F. Troxler, G.D. Offner

Heme oxygenase is an M_r 32,000 microsomal enzyme which catalyzes the rate-limiting step in the oxidative catabolism of heme to yield equimolar quantities of biliverdin IX, carbon monoxide, and iron. These investigations have provided evidence suggesting that immunochemical and structural differences exist between bovine spleen heme oxygenase and heme oxygenase enzymes from other mammalian species. Using an antibody directed against bovine spleen heme oxygenase, enzyme-linked immunosorbent assays, Western blotting experiments, and cell-free translation immunoprecipitation studies showed that bovine spleen heme oxygenase is only weakly immunochemically related to heme oxygenase from rat spleen. This observation was supported by the fact that a rat spleen heme oxygenase cDNA probe did not hybridize significantly to bovine spleen heme oxygenase mRNA in Northern analyses nor to restriction fragments containing the bovine heme oxygenase gene in Southern analyses. Tryptic peptides were prepared from bovine spleen heme oxygenase and the amino acid sequences of nine peptides comprising 94 amino acid residues were determined, providing the first information on the primary structure of bovine spleen heme oxygenase. Comparison of the sequences of these tryptic peptides with regions of the deduced amino acid sequences of rat spleen and human macrophage heme oxygenase revealed sequence similarities ranging from 55 to 100%. Several peptides displaying the highest degree of sequence similarity were found to occur in regions of the heme oxygenase molecule postulated to contain the heme binding site, indicating that despite the immunochemical and apparent structural differences between bovine spleen heme oxygenase and the rat and human enzymes, functionally important amino acid residues have been conserved in the evolution of mammalian heme oxygenase genes.

NATURAL ANTIBODY RECOGNITION OF v-H-ras INDUCED 10T½ TRANSFORMATION

David F. Tough, Donna A. Chow

An increasing body of evidence supports a role for natural antitumor antibodies against tumors in vivo. However, a role for natural antibodies (NAb) in tumor surveillance would imply that sensitivity to NAb should increase following events associated with cellular transformation. To test this prediction, we examined by flow cytometry the effect on serum NAb binding of v-H-ras expression and integration of 10T½. The co-introduction of v-H-ras and the neomycin resistance (neo^r) gene into 10T½ followed by G418 selection resulted in a marked and heterogeneous increase in NAb binding. Clonal analysis of this population demonstrated that the increased NAb binding was associated with tumorigenic conversion and ras-p21 expression. The results provide the first evidence for a NAb-susceptible phase of ras-induced transformation.

A STIMULATORY EFFECT OF INTERLEUKIN-1 ON ADRENOCORTICAL CORTISOL SECRETION MEDIATED BY PROSTAGLANDINS

J.S.D. Winter, K.W. Gow, Y.S. Perry and A.H. Greenberg

Studies using cultured bovine adrenocortical cells now demonstrate that the cytokines interleukin-1 (IL-1)α and β, contrary to previous reports, can stimulate cortisol secretion in vitro in a dose- and time-dependent fashion. However, detectable levels of IL-1 receptor could not be demonstrated in adrenal cortical, medullary, or capsular cells by membrane displacement of iodinated IL-1α by unlabeled IL-1β, a technique that readily demonstrates specific IL-1α-binding sites on 3T3 fibroblasts. The stimulatory effect of IL-1 on cortisol secretion could be totally blocked by indomethacin, an indication that this effect might be mediated indirectly via local release of prostaglandins (PGs). Subsequent investigations have confirmed that IL-1 does enhance the conversion of [^{3}H]arachidonate to PGs by cultured adrenal cells, and that some of these PGs (PGD$_2$, PGF$_2$, and PGE$_2$) in turn, can stimulate cortisol production. Taken together these observations suggest that IL-1-induced stimulation of cortisol secretion is mediated through local release of PGs by a small subpopulation of cells within the adrenal gland.

Publications

Atkinson, E.A., Gerrard, J.M., Hildes, G.E. and Greenberg, A.H. Studies of the Mechanism of Natural Killer (NK) Degranulation and Cytotoxicity. J. Leukocyte Biol. 47:39-48, 1990.

Bennet, R.D., Chow, D.A. Inverse correlation between natural antitumor antibodies and tumor susceptibility in individual xid-bearing mice. Nat. Immun. Cell Growth Regul. in press, 1990.

Brandes, L.J., Davie, J.R., Paraskevas, F., Sukhu, B., Bogdanovic, R.P. and LaBella, F.S.. The antiproliferative potency of histamine antagonists correlates with inhibition of binding of [^{3}H]-histamine to novel intracellular receptors (H_{IC}) in microsomal and nuclear fractions of rat liver. In: New Perspectives in Histamine Research (H. Timmerman and H. van der Goot, eds.) Agents and Actions (Suppl) 33:325-342, 1990.

Brandes, L.J., and Hogg, G.R. Study of the in vivo antioestrogen action ofN,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine.HCl (DPPE), a novel intracellular histamine antagonist and antioestrogen binding site ligand. J. Reprod. Fert., 89:59-67, 1990.

Brandes, L.J., LaBella, F.S., Glavin, G.B., Paraskevas, F., Saxena, S.P., McNicol, A. and Gerrard, J.M. Histamine as an Intracellular Messenger. Biochem. Pharmacol. 40:1677-1681, 1990

Brandes, L.J., Sukhu, B., and R.P. Bogdanovic. Does intracellular histamine mediate mast cell histamine release? Biochem. Biophys. Res. Commun., 167:665-672, 1990.

Brown, R., Zuo, L., Vriend, C., Janz, L., Falk, J., Nance, D.M., Dyck, D.and Greenberg, A.H. Adrenocortical and sympathetic pathways modulate splenic macrophage interleukin-1 secretion. Ann. N.Y. Acad. Sci., (1990).

Chow, D.A. RNK granule extract cytolysis: Differential inhibitor productionby an NK-resistant vs an NK-sensitive murine lymphoma. Cell. Immunol. 127: 172-186, 1990.

Chow, D.A. RNK cytotoxic granule extract: Differential sensitivity of an NK-sensitive and an NK-resistant murine lymphoma. Natural Killer Cells: Biology & Clinical Application.

Dyck, D.G. and Greenberg, A.H. Immunopharmacologic tolerance as a conditioned response: Dissecting the brain-immune pathway. In "Psychoneuroimmunology II" Ed. Ader, R., Felton, D.L. and Cohen, N. Academic Press, Orlando, p 663-684 (1990).

Dyck, D.G., Janz, L., Osachuk, T.A.G., Falk, J., Labensky, J. andGreenberg, A.H. The Pavlovian conditioning of IL-1-induced glucocorticoid secretion. Brain Behavior and Immunity, 4:93-104, (1990).

Gerrard, J.M., Singhroy, S., Duta, E., Nosek-Cenkowska, B., Israels, S.J.,Israels, E.D. Studies in patients with bleeding disorders show that platelet-vessel interaction is important for thromboxane formation in bleeding time wounds. Thrombos. Res. 60:7-859, 1990.

Houston, D.S., Robinson, P. and Gerrard, J.M. Inhibition of Intravascular Platelet Aggregation by Endothelium-Derived Relaxing Factor: Reversal by Red Blood Cells. Blood 76:953-958, 1990.

Israels, S.J., Daniels, M., McMillan, E.M. Deficient collagen-induced activation in the newborn platelet. Pediatr. Res. 27:337-343, 1990.

Israels, S.J., McNicol, A., Robertson, C., Gerrard, J.M. Platelet storage pool deficiency: Diagnosis in patients with prolonged bleeding times and normal platelet aggregation. Br. J. Haematol. 75:118-121, 1990.

McKenna, R.M., Richmond, K-A., Dodd, J.G., Chow, D.A. Postgraduate experience - The great sex divide in health sciences. The New England Journal of Medicine 323: 1637-1638, 1990.

Khalil, N., Battistuzzi, S.C., Kraut, R., Schwarz, L.C. and Greenberg, A.H. Growth factor initiated proliferation of mouse embryonic fibroblasts induces cytotoxicity by natural killer cells and by a non-cytolysin cytotoxin in natural killer granules, J. Immunol., 145:1286-1292, 1990.

Khalil, N., Bereznay, O., Sporn, M. and Greenberg, A.H. Transforming growth factor-β (TGF-β) production and immunohistochemical localization during bleomycin-induced pulmonary inflammation. In: Piez, K.A. and Sporn, M.B., eds. Transforming growth factor-βs: Chemistry, biology and therapeutics. Ann. N.Y. Acad. Sci., 593:350-352, 1990.

Khalil, N., O'Connor, R., Unruh, H., Warren, P., Kemp, A., Bereznay, O., Flanders, K. and Greenberg, A.H. Increased production and immunohistochemical localization of Transforming Growth Factor-beta (TGF-β) in idiopathic pulmonary fibrosis. Am. J. Resp. Cell. Mol. Biol.5:155,1991.

Khalil, N. and Greenberg, A.H. TGF-b in pulmonary fibrosis. In: Marsh,J. ed. Clinical Applications of TGF-β. Ciba Foundation Symposium, 1990; 157.

Kraut, R.P., Bose, D., Bose, R., Cragoe, E.J. Jr. and Greenberg, A.H. The influence of Na^+, Ca^{++} and the Na^+/Ca^{++} antiport on cytolysin/perforin mediated cytolysis. J. Immunol., 144:3498-3505, (1990).

Roussel, E., Gerrard, J.M. and Greenberg, A.H. Long-term cultures of human peripheral blood lymphocytes with recombinant human interleukin-2 generate a population of virtually pure $CD3^+CD16^-D56^-$ large granular lymphocyte LAK cells. Clin. Exp. Immunol. 82:416-421, 1990.

Saxena, S.P., McNicol, A., Brandes, L.J., Becker, A.B. and Gerrard, J.M. A Role for Intracellular Histamine in Collagen-Induced Platelet Aggregation. Blood 75:407-414, 1990.

Schacter, B.A., Cripps, V., Troxler, R.F., and G.D. Offner. Structural studies on bovine spleen heme oxygenase: Immunological and structural diversity among mammalian heme oxygenase enzymes. Arch. Biochem. Biophys., 282:404-412, 1990.

Tough, D., Chow, D.A. Natural antibody recognition of v-H-ras-induced 10T transformation. Nat. Immun. Cell Growth Regul. in press, 1990.

Winter, J.S.D., Gow, K.W., Perry, Y.S. and Greenberg, A.H. A stimulatory effect of interleukin-1 on adrenocortical cortisol secretion mediated by prostaglandins. Endocrinology, 127:1904-1909, (1990).

Published Abstracts

Israels, L.G., Jesson, M.I., Israels, S., Greenberg, A.H., Begleiter, A., Mowat, M.R.A., Johnston, J.B. Activity of TGF-β in chronic lymphocytic leukemia (CLL) in vitro. Blood 76:283a, 1990.

Israels, S.J., Kobrinsky, N.L. Intensive early therapy for non-metastatic osteosarcoma. American J. Ped. Hematology/Oncology, 12:114, 1990.

Khalil, N., Bereznay, O. and Greenberg, A.H. Alveolar macrophages from bleomycin-induced pulmonary inflammation synthesize and secrete transforming growth factor-beta (TGF-β). Am. Rev. Resp. Dis., 1990; 141:A138.

Khalil, N., O'Connor, R., Unruh, H., Warren, P., Kemp, A. and Greenberg, A.H. Enhanced expression and immunohistochemical distribution of transforming growth factor-beta (TGF-β) in idiopathic pulmonary fibrosis (IPF). Chest, 1991.

AUDITOR'S REPORT TO THE MEMBERS FOR THE YEAR ENDING MARCH 31, 1990

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a member firm of
Coopers & Lybrand (International)

June 13, 1991

AUDITORS' REPORT TO THE MEMBERS

We have audited the balance sheet of The Manitoba Cancer Treatment and Research Foundation as at March 31, 1991 and the statements of revenue and expenses and surplus of the General Account, the Trust and Research Account and the Building Account and the statement of Clinical Investigation Account transactions for the year then ended. These financial statements are the responsibility of the Foundation's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with generally accepted auditing standards. Those standards require that we plan and perform an audit to obtain reasonable assurance whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation.

Note 1 describes the policy adopted by the Foundation with respect to vacation pay. At March 31, 1991 revenue in the amount of $455,000 (1990 - $335,000) has been accrued. In our opinion, it is not appropriate under generally accepted accounting principles to anticipate revenue of the following year through accrual at the year end date. Had such revenue not been accrued, revenue and surplus for the year would have been reduced by $120,000 (1990 - $26,000) and assets would have been reduced by $455,000 (1990 - $335,000). In addition, surplus as at April 1, 1989 would have been reduced by $309,000.

In our opinion, except for the effects of the inappropriate accrual of revenue described in the preceding paragraph, these financial statements present fairly, in all material respects, the financial position of the Foundation as at March 31, 1991 and the results of its operations for the year then ended in accordance with generally accepted accounting principles.

Coopers & Lybrand

CHARTERED ACCOUNTANTS

THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

BALANCE SHEET AS AT MARCH 31, 1991

ASSETS

	1991 $	1990 $
	GENERAL ACCOUNT	
Cash	427,847	614,120
Short-term investments	729,344	700,321
Amounts owing by the Manitoba Health Services Commission (note 2)	67,684	70,182
Accounts receivable	175,447	18,068
Amounts receivable from Clinical Investigation Account	16,811	1,648
Prepaid expenses	57,287	85,947
Vacation pay recoverable	455,000	335,000
Equipment - at nominal value	1	1
	1,929,421	1,825,287
	TRUST AND RESEARCH ACCOUNT	
Cash	522,815	58,679
Accounts receivable and accrued interest	280,127	167,929
Amounts receivable from Clinical Investigation Account	40,111	-
Amounts receivable from General Account	1,453	16,690
Investments - at cost	6,787,965	7,355,520
	7,632,471	7,598,818
	BUILDING ACCOUNT	
Cash	233,152	1,084,274
Accounts receivable	37,547	4,093
Amounts receivable from General Account	-	18,919
Amounts receivable from Trust and Research Account	-	365
Investments - at cost	5,098,995	1,786,416
Fixed assets	220,000	-
	5,589,694	2,894,267
	CLINICAL INVESTIGATION ACCOUNT	
Cash	391,930	293,726
Short-term investments	199,208	-
Accounts receivable	115,623	64,514
Amounts receivable from Trust and Research Account	9,899	2,155
	716,660	360,395

SIGNED ON BEHALF OF THE FOUNDATION

Member

Member

LIABILITIES

	1991 $	1990 $
Accounts payable and accrued liabilities	965,863	957,152
Amounts payable to Trust and Research Account	1,453	16,690
Amounts payable to Building Account	-	18,919
	967,316	992,761
Surplus	962,105	832,526
	1,929,421	1,825,287
Accounts and grants payable	172,077	639,007
Amounts payable to Building Account	-	565
Amounts payable to Clinical Investigation Account	9,899	2,155
Research fund	7,450,495	6,957,091
	7,632,471	7,598,818
Accounts payable and accrued liabilities	14,297	11,174
Building fund	5,575,397	2,883,093
	5,589,694	2,894,267
Accounts payable and accrued liabilities	154,764	182,403
Amounts payable to Trust and Research Account	40,111	-
Amounts payable to General Account	16,811	1,648
Commitments payable	504,974	176,344
	716,660	360,395

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

GENERAL ACCOUNT

STATEMENT OF REVENUE AND EXPENSES AND SURPLUS

FOR THE YEAR ENDED MARCH 31, 1991

	1991 $	1990 $
REVENUE		
Manitoba Health Services Commission	10,061,031	9,347,095
Recoveries from other institutions	50,721	46,602
	10,111,752	9,393,697
EXPENSES		
Operating expenses -		
Salaries and benefits	8,096,642	7,428,951
Building occupancy	716,575	724,742
General expenses	609,812	508,342
Supplies and other departmental expenses	269,668	244,089
Diagnostic services	235,628	204,781
	9,928,325	9,110,905
Equipment purchases	190,239	283,709
	10,118,564	9,394,614
EXCESS OF EXPENSES OVER REVENUE	6,812	917
OTHER INCOME - net of unfunded costs (note 3)	136,391	132,607
SURPLUS FOR THE YEAR	129,579	131,690
SURPLUS - BEGINNING OF YEAR	832,526	700,836
SURPLUS - END OF YEAR	962,105	832,526

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

TRUST AND RESEARCH ACCOUNT

STATEMENT OF REVENUE AND EXPENSES AND SURPLUS

FOR THE YEAR ENDED MARCH 31, 1991

	1991 $	1990 $
REVENUE		
Donations	119,558	151,005
Investment income	819,788	796,263
Transfer from General Account	-	15,500
	939,346	962,768
EXPENSES		
Cell Biology	300,000	300,000
Research grants and personnel awards	181,791	117,392
Chemotherapy advisory system	-	478,650
Equipment	6,792	45,734
Staff co-ordinator	-	28,800
Miscellaneous	(2,530)	8,315
	486,053	978,891
EXCESS OF REVENUE OVER EXPENSES (EXPENSES OVER REVENUE)	453,293	(16,123)
FUND BALANCE - BEGINNING OF YEAR	6,957,091	7,714,214
	7,410,384	7,698,091
TRANSFER TO BUILDING ACCOUNT (note 4)	-	(741,000)
TRANSFER FROM CLINICAL INVESTIGATION ACCOUNT (note 5)	40,111	-
FUND BALANCE - END OF YEAR	7,450,495	6,957,091

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

BUILDING ACCOUNT

STATEMENT OF REVENUE AND EXPENSES AND SURPLUS

FOR THE YEAR ENDED MARCH 31, 1991

	1991 $	1990 $
REVENUE		
Donations	2,187,882	1,927,378
Lottery - net of expenses of $911,478 (1990 - $813,726)	453,022	686,274
Investment income	485,072	189,187
	3,125,976	2,802,839
EXPENSES		
Direct mail campaign	228,961	375,645
Fundraising consultant fees	42,000	94,500
Salaries and benefits	78,274	77,898
Printing, stationery and brochures	19,473	31,730
Computer services	2,771	26,293
Equipment	26,186	25,556
Miscellaneous	36,007	29,124
	433,672	660,746
EXCESS OF REVENUE OVER EXPENSES	2,692,304	2,142,093
FUND BALANCE - BEGINNING OF YEAR	2,883,093	-
	5,575,397	2,142,093
TRANSFER FROM TRUST AND RESEARCH ACCOUNT (note 4)	-	741,000
FUND BALANCE - END OF YEAR	5,575,397	2,883,093

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

STATEMENT OF CLINICAL INVESTIGATION ACCOUNT TRANSACTIONS

FOR THE YEAR ENDED MARCH 31, 1991

	1991 $	1990 $
RECEIPTS		
Grants received	1,461,736	960,996
Investment income	36,811	30,710
Royalties	1,311	5,360
Proceeds on transfer of techology	43,144	15,917
	1,543,502	1,012,983
DISBURSEMENTS		
Administrative costs	39,644	50,898
Associated Institutions - salary support	205,579	189,419
Clinical Investigation Office	161,117	149,456
Lung cancer studies	174,888	120,832
Other studies of less than $20,000	85,708	87,763
Outreach Network	24,137	75,342
Theraplan modification	33,748	60,732
Royalties	905	2,680
On-line verification of radiation treatment	122,432	58,107
Chemotherapy Advisory System	165,089	47,299
Electron Dosimetry	-	46,249
Moly Extraction System	5,535	45,631
On-line portal imaging	68,595	33,829
Effect of Estradiol and Tamoxifen on Lymphocytes	7,464	25,084
Radiotherapy portal verification and rectification	10,119	17,383
Experimental hyperthermia	-	10,751
Lung study - Epidemiology	25,467	15,423
Studies with Deoxycoformycin	22,781	1,028
Lymphocyte reactions to estradiol and tamoxifen	21,553	-
	1,174,761	1,037,906
EXCESS OF RECEIPTS OVER DISBURSEMENTS (DISBURSEMENTS OVER RECEIPTS)	368,741	(24,923)
TRANSFER TO TRUST AND RESEARCH ACCOUNT (note 5)	(40,111)	-
	328,630	(24,923)
COMMITMENTS PAYABLE - BEGINNING OF YEAR	176,344	201,267
COMMITMENTS PAYABLE - END OF YEAR	504,974	176,344

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

NOTES TO FINANCIAL STATEMENTS

FOR THE YEAR ENDED MARCH 31, 1991

1. SIGNIFICANT ACCOUNTING POLICIES

The financial statements of the Foundation are prepared in accordance with generally accepted accounting principles for non-profit organizations and reflect the following policies:

(a) Equipment

Annual expenditures for equipment acquisitions are charged directly to operations.

(b) Fixed assets

Fixed assets have been purchased for the Foundation's planning offices during the planning and construction of the new facilities. They have been recorded at cost and will be depreciated over a period of five years commencing in the year ending March 31, 1992.

(c) Investments

Investments are recorded at cost with any premium or discount being amortized over the term of the investment.

(d) Revenue

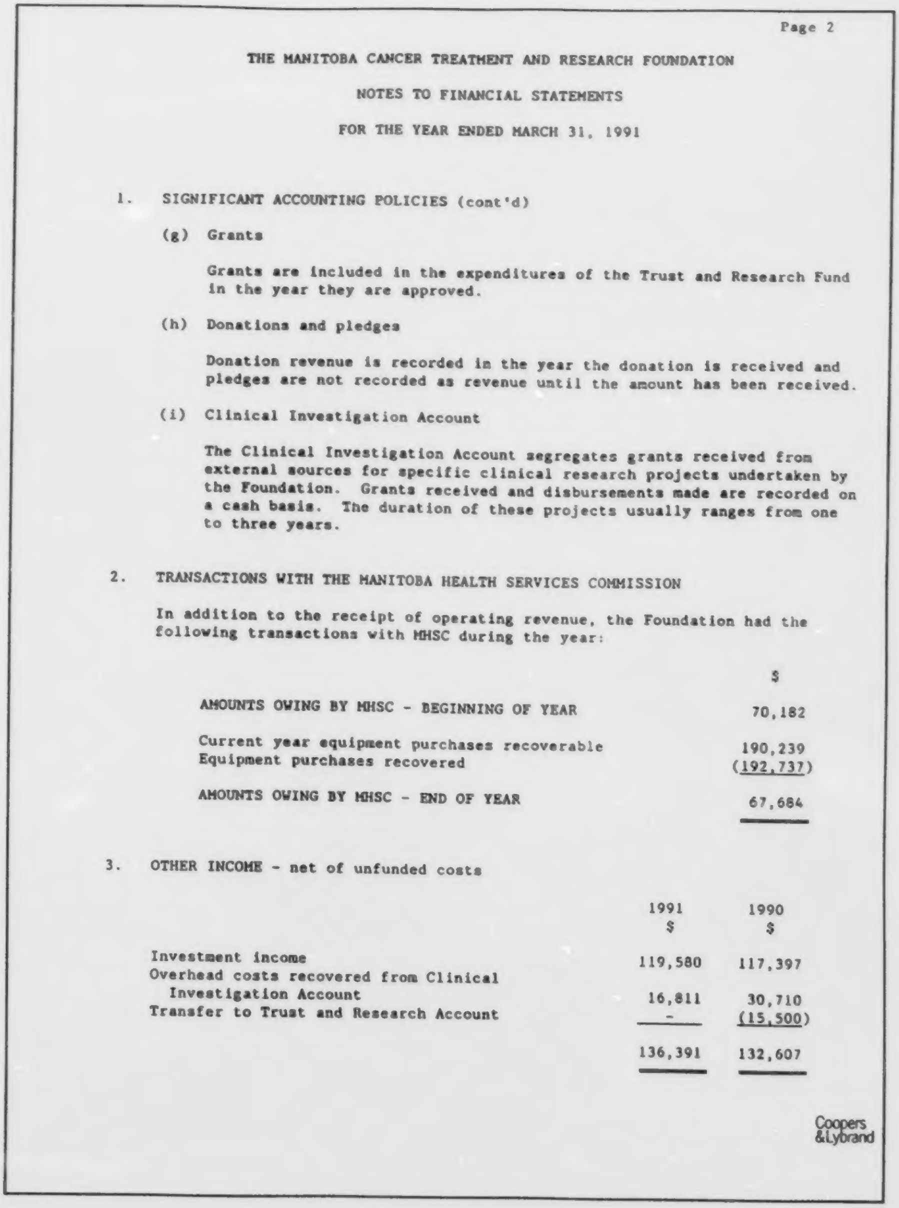
Revenue received from the Manitoba Health Services Commission (MHSC) for net insured patient costs is based on operating budget amounts approved annually and adjusted for amounts to be returned to or recovered from the commission in respect of surplus or deficit arising in the current fiscal year.

(e) Vacation pay

The Foundation recognizes the expense and accrues the liability owing to its employees for vacation pay entitlements as of the year end. The Foundation also accrues income from MHSC relating to this vacation pay liability. Vacation pay is included as part of MHSC's global funding in the following fiscal year when the vaction pay costs normally occur.

(f) Surplus

The Foundation is entitled to retain surpluses arising from excess of revenue over approved expenses for each fiscal year up to a maximum of 2% of the net insured patient costs. Any surplus amount in excess of the maximum is returned to the Manitoba Health Services Commission.



THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

NOTES TO FINANCIAL STATEMENTS

FOR THE YEAR ENDED MARCH 31, 1991

1. SIGNIFICANT ACCOUNTING POLICIES (cont'd)

(g) Grants

Grants are included in the expenditures of the Trust and Research Fund in the year they are approved.

(h) Donations and pledges

Donation revenue is recorded in the year the donation is received and pledges are not recorded as revenue until the amount has been received.

(i) Clinical Investigation Account

The Clinical Investigation Account segregates grants received from external sources for specific clinical research projects undertaken by the Foundation. Grants received and disbursements made are recorded on a cash basis. The duration of these projects usually ranges from one to three years.

2. TRANSACTIONS WITH THE MANITOBA HEALTH SERVICES COMMISSION

In addition to the receipt of operating revenue, the Foundation had the following transactions with MHSC during the year:

	$
AMOUNTS OWING BY MHSC - BEGINNING OF YEAR	70,182
Current year equipment purchases recoverable	190,239
Equipment purchases recovered	(192,737)
AMOUNTS OWING BY MHSC - END OF YEAR	67,684

3. OTHER INCOME - net of unfunded costs

	1991 $	1990 $
Investment income	119,580	117,397
Overhead costs recovered from Clinical Investigation Account	16,811	30,710
Transfer to Trust and Research Account	-	(15,500)
	136,391	132,607

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THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

NOTES TO FINANCIAL STATEMENTS

FOR THE YEAR ENDED MARCH 31, 1991

4. BUILDING ACCOUNT

On May 1, 1989, the Foundation initiated a fundraising campaign aimed at raising capital for the expansion of existing facilities. The preliminary costs of the expansion are estimated at $15,000,000.

A separate fund has been created to record the transactions of this fundraising campaign and all unrestricted donations received in the period from May 1, 1989 to March 31, 1991 were recorded in this account. In addition, a transfer of $741,000 from the Trust and Research Account to the Building Account was approved by the Board in 1989.

5. TRUST AND RESEARCH ACCOUNT

During the year, the Clinical Investigation Account transferred to the Trust and Research Account net proceeds of $40,111 resulting from the transfer of technology to third parties.

SCHEDULE A

THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

TRUST AND RESEARCH ACCOUNT

SCHEDULE OF INVESTMENTS AS AT MARCH 31, 1991

	Book value $	Market value $
Bonds, debentures and guaranteed investment certificates -		
B.C. Telephone Company -		
9.875%, November 1, 2003	50,000	47,350
Canadian Imperial Bank of Commerce -		
13.00%, June 3, 1992	249,725	257,750
City of Edmonton coupons -		
June 13, 1992	34,250	33,778
December 13, 1992	97,712	95,829
City of Winnipeg -		
10.00%, February 23, 1993	165,276	170,085
Government of Canada -		
9.75%, May 1, 1991	199,949	199,900
10.875%, November 1, 1991	36,756	36,855
9.25%, July 1, 1992	199,236	199,300
10.93%, November 1, 1992	104,900	106,210
10.75%, May 1, 1993	453,192	468,534
9.25%, May 15, 1997	100,000	98,950
9.25%, May 15, 1997	100,000	98,950
Government of Canada Treasury Bills -		
9.450%, May 3, 1991	453,133	453,133
Investors Group Debentures -		
9.875%, October 4, 1998	50,000	47,925
Montreal Trust -		
13.50%, April 15, 1991	500,000	500,000
11.25%, October 2, 1995	20,000	20,000
Carried forward	2,814,129	2,834,549

SCHEDULE A
Page 2

THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

TRUST AND RESEARCH ACCOUNT

INVESTMENTS AS AT MARCH 31, 1991

	Book value $	Market value $
Brought forward	2,814,129	2,834,549
Bonds, debentures and guaranteed investment certificates (cont'd) -		
Ontario Hydro Bonds -		
10.75%, December 15, 1992	199,702	202,600
9.75%, January 15, 1993	598,686	600,300
9.50%, February 10, 2000	400,000	382,800
Province of Manitoba -		
9.740%, May 29, 1991	393,848	393,848
Royal Bank of Canada -		
12.25%, May 3, 1993	396,568	400,000
10%, December 1, 1994	160,000	158,320
Royal Trust -		
9.625%, May 1, 1991	10,000	10,000
13.25%, May 3, 1993	529,407	529,407
11.25%, December 13, 1993	225,028	225,028
11.38%, December 19, 1993	500,000	500,000
11%, December 21, 1993	10,005	10,005
12.13%, March 30, 1994	200,000	200,000
10.9%, August 15, 1994	200,592	200,000
10.75%, December 19, 1995	150,000	150,000
	6,787,965	6,796,857

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SCHEDULE B

THE MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

BUILDING ACCOUNT

INVESTMENTS AS AT MARCH 31, 1991

	Book value $	Market value $
Bonds, debentures and guaranteed investment certificates -		
Government of Canada Treasury Bills -		
10.50%, April 26, 1991	2,643,553	2,643,553
9.65%, June 7, 1991	754,520	754,520
General Motors Acceptance Corporation - 11.30%, February 1, 1993	547,330	544,655
Royal Bank of Canada - 9.60%, May 24, 1991	463,467	463,467
Toronto-Dominion Bank - 9.70%, May 24, 1991	690,125	690,125
	5,098,995	5,096,320

Coopers & Lybrand

1990 ANNUAL REPORT
STATISTICS

MANITOBA CANCER TREATMENT AND RESEARCH FOUNDATION

CANCER

INCIDENCE and MORTALITY

in the PROVINCE of MANITOBA

DURING the CALENDAR YEAR of 1990

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INTRODUCTION

The Manitoba Cancer Treatment and Research Foundation is mandated to collect, register and maintain data on all cancer cases in Manitoba. The Central Cancer Registry is the repository for data received from a wide array of primary sources including pathology/cytology reports, admission/ separation data from the hospital abstracting system of the Manitoba Health Services Commission, death registration data from the Department of Vital Statistics and clinical data from individual physicians' offices.

Incidence and mortality data for the calendar year of 1990 are presented in tabular and graphic formats.

Table Ia identifies the distribution of new cancer cases by location of diagnosis. The latter party of the table provides the distribution of registered cancer deaths by health care facility.

Table Ib specifies the urban (Winnipeg), rural and out-of-province distribution of newly diagnosed cancer cases and registered cancer deaths.

Table II represents incidence and mortality data by age and Statistics Canada census division. Cancer incidence and mortality rates per 100,000 population are provided. Rates are obtained by dividing the number of cases (incidence or mortality) for a specific census division by the 1986 Statistics Canada census figures for that division, multiplied by 100,000. The map opposite Table II correlates census division number with its geographic location.

Table III describes cancer incidence and mortality by age and sex. Cancer rates are obtained by dividing the number of cases (incidence or mortality) for a specific age group by the respective Statistics Canada population estimates for 1990, multiplied by 100,000.

Tables IV through XVI provide the age and sex distribution of cancer incidence and mortality by anatomical region, using the International Classification of Disease (9th Revision - Clinical Modification). Rates are calculated in the same manner as in Table III.

Table XVII summarizes the cancer incidence information presented in Tables IV through XVI.

Twenty-Year Trends for incidence and mortality rates are presented graphically for females, males and the total cancer population by anatomical region of the body.

1990 TABLE Ia PLACE

DIAGNOSIS	Male	Female	Total
Health Sciences Centre	524	639	1,163
St. Boniface General Hospital	458	480	938
Other Hospitals in Winnipeg	1,017	952	1,969
Other Hospitals in Manitoba	791	722	1,513
Hospitals Outside Manitoba	46	71	117
Doctors and Clinics	694	760	1,454
TOTAL	**3,530**	**3,624**	**7,154**

DEATH	Male	Female	Total
Hospitals- Winnipeg	*722*	*661*	*1,383*
Hospitals-Outside Winnipeg	*420*	*274*	*694*
Nursing Homes	*47*	*58*	*105*
Other- Winnipeg	*49*	*36*	*85*
Other-Outside Greater Winnipeg	*44*	*31*	*75*
TOTAL	**1,282**	**1,060**	**2,342**

1990 TABLE Ib RESIDENCE

DIAGNOSIS	Male	Female	Total
Winnipeg	1,900	2,150	4,050
Manitoba- Outside Winnipeg	1,524	1,344	2,868
Non-Manitoba Residence	98	122	220
Residence Unknown	8	8	16
TOTAL	**3,530**	**3,624**	**7,154**

DEATH	Male	Female	Total
Winnipeg	*779*	*710*	*1,489*
Manitoba- Outside Winnipeg	*485*	*333*	*818*
Non-Manitoba Residence	*18*	*17*	*35*
Residence Unknown	*0*	*0*	*0*
TOTAL	**1,282**	**1,060**	**2,342**

1990 TABLE II AGE and SEX DISTRIBUTION

INCIDENCE

Age Group	Male	Rate	Female	Rate	TOTAL	RATE
0 - 4	14	32.5	10	24.3	24	28.5
5 - 9	7	17.1	5	13.0	12	15.1
10 - 14	4	10.1	2	5.3	6	7.1
15 - 19	6	14.5	22	56.2	28	34.8
20 - 24	9	21.2	81	201.4	90	109.0
25 - 29	28	57.8	152	318.6	180	187.3
30 - 34	42	90.5	171	375.8	213	231.7
35 - 39	38	91.5	162	384.7	200	239.2
40 - 44	76	207.0	165	447.1	241	327.4
45 - 49	120	422.5	159	559.8	279	491.1
50 - 54	134	560.6	197	814.0	331	688.1
55 - 59	237	1,030.4	253	1,076.5	490	1,053.7
60 - 64	392	1,757.8	312	1,305.4	704	1,523.8
65 - 69	550	2,696.0	427	1,721.7	977	2,161.5
70 - 74	589	3,704.4	392	1,931.0	981	2,709.9
75 - 79	557	4,565.5	408	2,358.3	965	3,271.1
80 - 84	372	5,314.2	327	2,868.4	699	3,798.9
85 - 89	182	5,352.9	161	2,476.9	343	3,464.6
90 and over	69	5,750.0	86	2,457.1	155	3,297.8
Unknown	1	0.0	1	0.0	2	0.0
TOTAL	**3,427**	**637.7**	**3,493**	**632.3**	**6,920**	**634.9**

MORTALITY

Age Group	Male	Rate	Female	Rate	TOTAL	RATE
0 - 4	1	2.3	1	2.4	2	2.3
5 - 9	2	4.9	2	5.2	4	5.0
10 - 14	1	2.5	0	0.0	1	1.2
15 - 19	2	4.8	0	0.0	2	2.4
20 - 24	2	4.7	0	0.0	2	2.4
25 - 29	5	10.3	7	14.6	12	12.4
30 - 34	2	4.3	4	8.7	6	6.5
35 - 39	13	31.3	13	30.8	26	31.1
40 - 44	9	24.5	14	37.9	23	31.2
45 - 49	28	98.5	42	147.8	70	123.2
50 - 54	41	171.5	55	227.2	96	199.5
55 - 59	88	382.6	75	319.1	163	350.5
60 - 64	143	641.2	95	397.4	238	515.1
65 - 69	197	965.6	131	528.2	328	725.6
70 - 74	217	1,364.7	141	694.5	358	988.9
75 - 79	209	1,713.1	162	936.4	371	1,257.6
80 - 84	165	2,357.1	144	1,263.1	309	1,679.3
85 - 89	93	2,735.2	95	1,461.5	188	1,898.9
90 and over	46	3,833.3	62	1,771.4	108	2,297.8
Unknown	0	0.0	0	0.0	0	0.0
TOTAL	**1,264**	**235.2**	**1,043**	**188.7**	**2,307**	**211.6**

1990 TABLE III RESIDENTIAL DISTRIBUTION

INCIDENCE

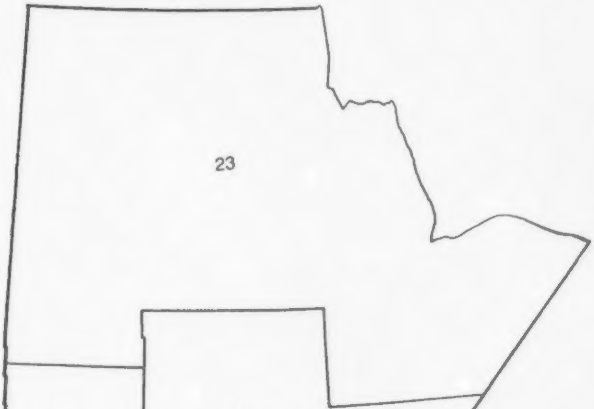
Residence	Male	Rate	Female	Rate	TOTAL	RATE
Division 1	69	821.4	67	852.4	136	836.4
Division 2	93	454.5	115	577.5	208	515.2
Division 3	122	641.2	99	510.4	221	575.2
Division 4	65	1,113.0	39	693.3	104	907.1
Division 5	76	917.3	64	779.5	140	848.7
Division 6	41	732.1	32	573.9	73	653.2
Division 7	195	698.7	216	739.5	411	719.6
Division 8	66	974.1	25	387.5	91	688.0
Division 9	77	667.2	60	512.8	137	589.5
Division 10	13	339.4	8	228.2	21	286.2
Winnipeg	1,867	650.6	2,022	657.3	3,889	654.1
Division 12	53	651.9	33	426.6	86	542.0
Division 13	67	394.6	97	582.7	164	487.8
Division 14	41	533.8	38	540.1	79	536.8
Division 15	105	875.7	85	718.5	190	797.6
Division 16	50	925.9	36	695.6	86	813.2
Division 17	121	907.7	78	591.3	199	750.3
Division 18	95	843.3	66	614.5	161	731.6
Division 19	5	105.3	11	251.1	16	175.3
Division 20	46	736.5	28	465.8	74	603.8
Division 21	54	440.9	48	406.0	102	423.8
Division 22	29	184.3	26	175.4	55	180.0
Division 23	10	184.3	9	186.1	19	185.1
TOTAL	**3,360**	**641.5**	**3,302**	**612.3**	**6,662**	**626.7**

MORTALITY

Residence	Male	Rate	Female	Rate	TOTAL	RATE
Division 1	*19*	*226.1*	*20*	*254.4*	*39*	*239.8*
Division 2	*29*	*141.7*	*23*	*115.5*	*52*	*128.8*
Division 3	*58*	*304.8*	*36*	*185.6*	*94*	*244.6*
Division 4	*21*	*359.5*	*6*	*106.6*	*27*	*235.4*
Division 5	*24*	*289.6*	*11*	*133.9*	*35*	*212.1*
Division 6	*11*	*196.4*	*7*	*125.5*	*18*	*161.0*
Division 7	*68*	*243.6*	*65*	*222.5*	*133*	*232.8*
Division 8	*6*	*88.5*	*6*	*93.0*	*12*	*90.7*
Division 9	*30*	*259.9*	*17*	*145.2*	*47*	*202.2*
Division 10	*0*	*0.0*	*2*	*57.0*	*2*	*27.2*
Winnipeg	*779*	*271.4*	*710*	*230.8*	*1,489*	*250.4*
Division 12	*15*	*184.5*	*8*	*103.4*	*23*	*144.9*
Division 13	*35*	*206.1*	*34*	*204.2*	*69*	*205.2*
Division 14	*15*	*195.3*	*7*	*99.5*	*22*	*149.5*
Division 15	*43*	*358.6*	*15*	*126.7*	*58*	*243.4*
Division 16	*12*	*222.2*	*8*	*154.5*	*20*	*189.1*
Division 17	*47*	*352.5*	*33*	*250.1*	*80*	*301.6*
Division 18	*18*	*159.7*	*17*	*158.2*	*35*	*159.0*
Division 19	*1*	*21.0*	*1*	*22.8*	*2*	*21.9*
Division 20	*11*	*176.1*	*2*	*33.2*	*13*	*106.0*
Division 21	*11*	*89.8*	*12*	*101.5*	*23*	*95.5*
Division 22	*9*	*57.2*	*3*	*20.2*	*12*	*39.2*
Division 23	*2*	*36.8*	*0*	*0.0*	*2*	*19.4*
TOTAL	**1,264**	**241.3**	**1,043**	**193.4**	**2,307**	**217.0**

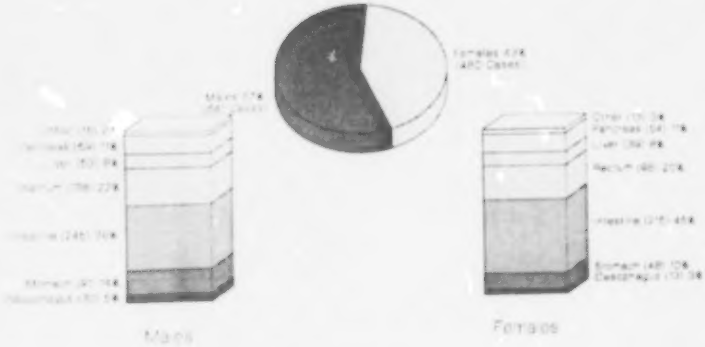
NOTE: **Rates are based on Statistics Canada 1986 Census Data**

STATISTICS CANADA
Standard Geographical Classification
Manitoba Census Divisions (1976)

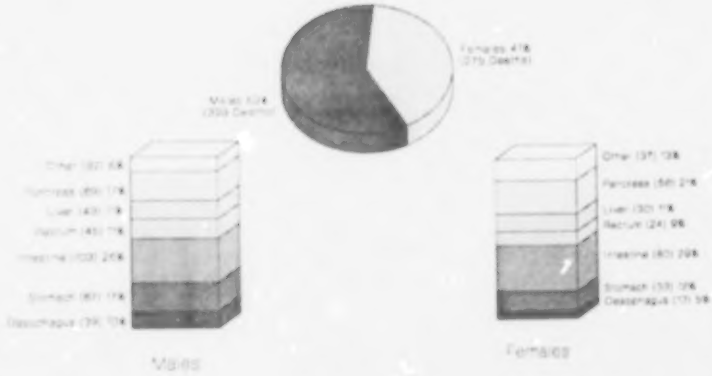


Digestive System 1990

Incidence



Mortality



1990 TABLE IV DIGESTIVE SYSTEM

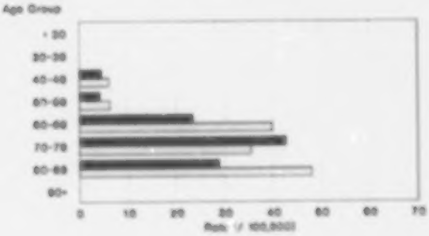
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	7	2.7	6	2.4	13	2.6
30-39	7	7.9	6	6.8	13	7.4
40-49	43	66.0	18	27.5	61	46.7
50-59	66	140.7	55	115.3	121	127.9
60-69	157	367.6	131	268.9	288	315.0
70-79	225	800.7	142	377.6	367	558.5
80-89	123	1,182.6	103	575.4	226	798.5
90 and over	12	1,000.0	19	542.8	31	659.5
Age not stated	1	0.0	0	0.0	1	0.0
TOTAL	**641**	**119.2**	**480**	**86.8**	**1,121**	**102.8**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*2*	*0.7*	*0*	*0.0*	*2*	*0.4*
30-39	*3*	*3.4*	*2*	*2.2*	*5*	*2.8*
40-49	*14*	*21.5*	*11*	*16.8*	*25*	*19.1*
50-59	*34*	*72.4*	*27*	*56.6*	*61*	*64.4*
60-69	*111*	*259.9*	*58*	*119.0*	*169*	*184.9*
70-79	*137*	*487.5*	*80*	*212.7*	*217*	*330.2*
80-89	*84*	*807.6*	*74*	*413.4*	*158*	*558.3*
90 and over	*13*	*1,083.3*	*23*	*657.1*	*36*	*765.9*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**398**	**74.0**	**275**	**49.7**	**673**	**61.7**

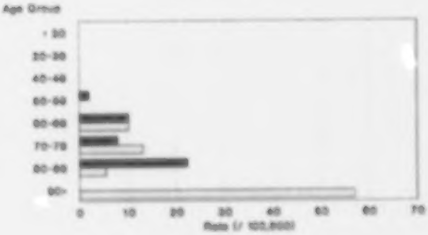
INCIDENCE & MORTALITY 1990

Oesophagus

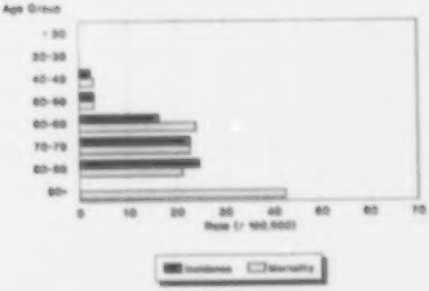
Males



Females



Total Population



1990 TABLE IVa OESOPHAGUS

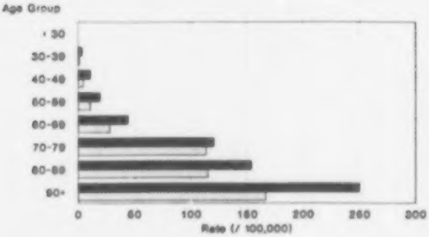
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	0	0.0	0	0.0
30-39	0	0.0	0	0.0	0	0.0
40-49	3	4.6	0	0.0	3	2.3
50-59	2	4.2	1	2.0	3	3.1
60-69	10	23.4	5	10.2	15	16.4
70-79	12	42.7	3	7.9	15	22.8
80-89	3	28.8	4	22.3	7	24.7
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**30**	**5.5**	**13**	**2.3**	**43**	**3.9**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*4*	*6.1*	*0*	*0.0*	*4*	*3.0*
50-59	*3*	*6.3*	*0*	*0.0*	*3*	*3.1*
60-69	*17*	*39.8*	*5*	*10.2*	*22*	*24.0*
70-79	*10*	*35.5*	*5*	*13.2*	*15*	*22.8*
80-89	*5*	*48.0*	*1*	*5.5*	*6*	*21.2*
90 and over	*0*	*0.0*	*2*	*57.1*	*2*	*42.5*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**39**	**7.2**	**13**	**2.3**	**52**	**4.7**

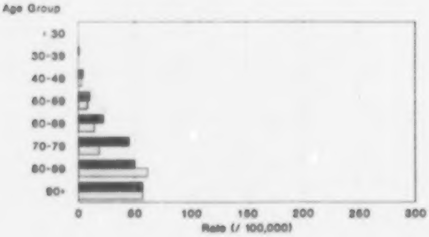
INCIDENCE & MORTALITY 1990

Stomach

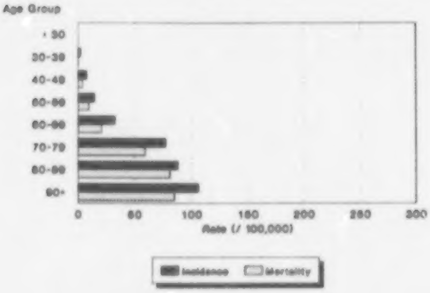
Males



Females



Total Population



1990 TABLE IVb STOMACH

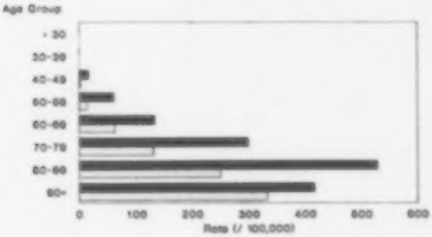
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	0	0.0	0	0.0
30-39	3	3.4	1	1.1	4	2.2
40-49	7	10.7	3	4.5	10	7.6
50-59	9	19.1	5	10.4	14	14.7
60-69	19	44.4	11	22.5	30	32.8
70-79	34	120.9	17	45.2	51	77.6
80-89	16	153.8	9	50.2	25	88.3
90 and over	3	250.0	2	57.1	5	106.3
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**91**	**16.9**	**48**	**8.6**	**139**	**12.7**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*1*	*1.1*	*0*	*0.0*	*1*	*0.5*
40-49	*3*	*4.6*	*2*	*3.0*	*5*	*3.8*
50-59	*5*	*10.6*	*4*	*8.3*	*9*	*9.5*
60-69	*12*	*28.1*	*7*	*14.3*	*19*	*20.7*
70-79	*32*	*113.8*	*7*	*18.6*	*39*	*59.3*
80-89	*12*	*115.3*	*11*	*61.4*	*23*	*81.2*
90 and over	*2*	*166.6*	*2*	*57.1*	*4*	*85.1*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**67**	**12.4**	**33**	**5.9**	**100**	**9.1**

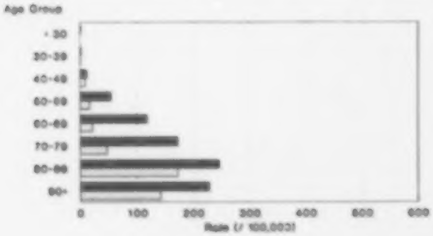
INCIDENCE & MORTALITY 1990

Large Bowel

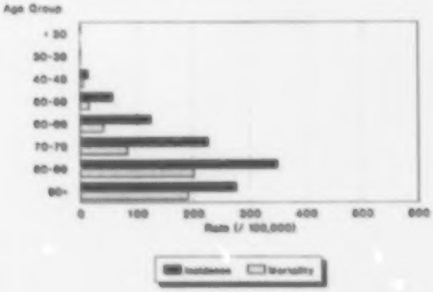
Males



Females



Total Population



1990 TABLE IVc LARGE BOWEL

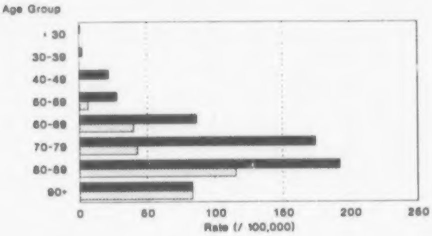
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	2	0.7	4	1.6	6	1.2
30-39	1	1.1	2	2.2	3	1.7
40-49	11	16.8	8	12.2	19	14.5
50-59	29	61.8	26	54.5	55	58.1
60-69	57	133.4	58	119.0	115	125.8
70-79	84	298.9	65	172.8	149	226.7
80-89	55	528.8	44	245.8	99	349.8
90 and over	5	416.6	8	228.5	13	276.5
Age not stated	1	0.0	0	0.0	1	0.0
TOTAL	**245**	**45.5**	**215**	**38.9**	**460**	**42.2**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*2*	*3.0*	*6*	*9.1*	*8*	*6.1*
50-59	*7*	*14.9*	*8*	*16.7*	*15*	*15.8*
60-69	*27*	*63.2*	*11*	*22.5*	*38*	*41.5*
70-79	*37*	*131.6*	*18*	*47.8*	*55*	*83.7*
80-89	*26*	*250.0*	*31*	*173.1*	*57*	*201.4*
90 and over	*4*	*333.3*	*5*	*142.8*	*9*	*191.4*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**103**	**19.1**	**80**	**14.4**	**183**	**16.7**

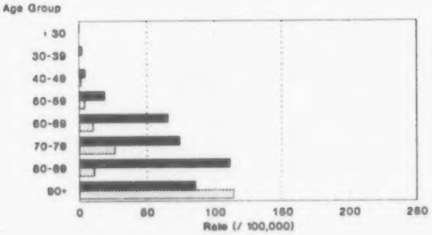
INCIDENCE & MORTALITY 1990

Rectum

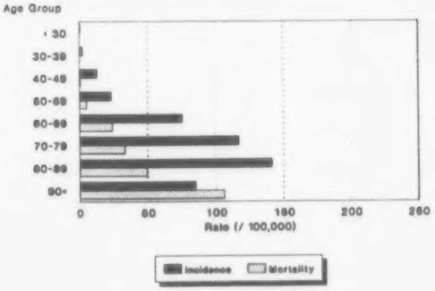
Males



Females



Total Population



1990 TABLE IVd RECTUM and RECTOSIGMOID JUNCTION

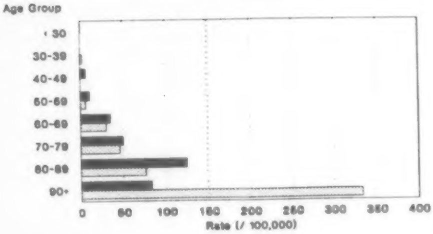
INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	2	0.7	1	0.4	3	0.6
30-39	2	2.2	2	2.2	4	2.2
40-49	14	21.5	3	4.5	17	13.0
50-59	13	27.7	9	18.8	22	23.2
60-69	37	86.6	32	65.7	69	75.4
70-79	49	174.3	28	74.4	77	117.1
80-89	20	192.3	20	111.7	40	141.3
90 and over	1	83.3	3	85.7	4	85.1
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**138**	**25.6**	**98**	**17.7**	**236**	**21.6**

MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*1*	*1.5*	*1*	*0.7*
50-59	*3*	*6.3*	*2*	*4.1*	*5*	*5.2*
60-69	*17*	*39.8*	*5*	*10.2*	*22*	*24.0*
70-79	*12*	*42.7*	*10*	*26.5*	*22*	*33.4*
80-89	*12*	*115.3*	*2*	*11.1*	*14*	*49.4*
90 and over	*1*	*83.3*	*4*	*114.2*	*5*	*106.3*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**45**	**8.3**	**24**	**4.3**	**69**	**6.3**

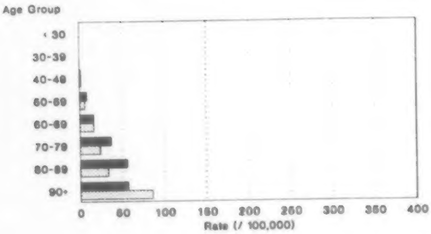
INCIDENCE & MORTALITY 1990

Liver

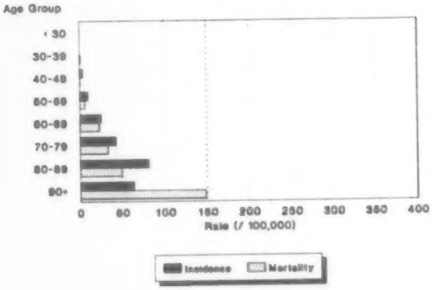
Males



Females



Total Population



1990 TABLE IVe LIVER and BILIARY PASSAGES*

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	0	0.0	1	0.2
30-39	0	0.0	0	0.0	0	0.0
40-49	4	6.1	1	1.5	5	3.8
50-59	5	10.6	4	8.3	9	9.5
60-69	15	35.1	8	16.4	23	25.1
70-79	14	49.8	14	37.2	28	42.6
80-89	13	125.0	10	55.8	23	81.2
90 and over	1	83.3	2	57.1	3	63.8
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**53**	**9.8**	**39**	**7.0**	**92**	**8.4**

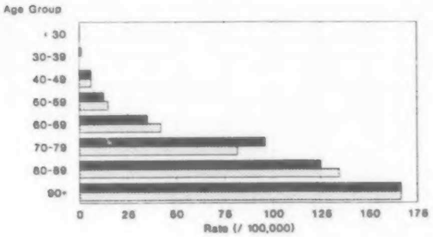
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*2*	*2.2*	*0*	*0.0*	*2*	*1.1*
40-49	*0*	*0.0*	*1*	*1.5*	*1*	*0.7*
50-59	*3*	*6.3*	*3*	*6.2*	*6*	*6.3*
60-69	*13*	*30.4*	*8*	*16.4*	*21*	*22.9*
70-79	*13*	*46.2*	*9*	*23.9*	*22*	*33.4*
80-89	*8*	*76.9*	*6*	*33.5*	*14*	*49.4*
90 and over	*4*	*333.3*	*3*	*85.7*	*7*	*148.9*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**43**	**8.0**	**30**	**5.4**	**73**	**6.6**

* This table probably includes a number of cases of secondary metastatic disease - not defined in the death certificate.

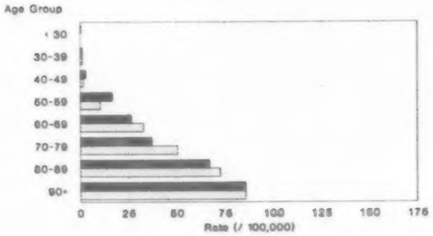
INCIDENCE & MORTALITY 1990

Pancreas

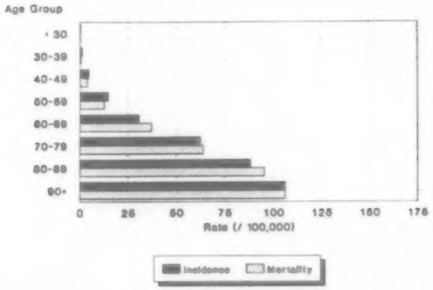
Males



Females



Total Population



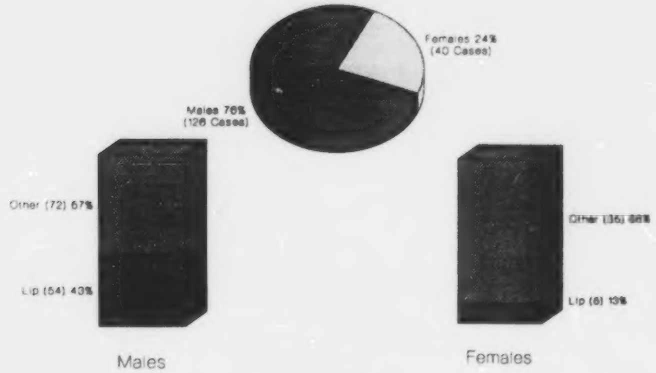
1990 TABLE IVf PANCREAS

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	1	0.4	2	0.4
30-39	1	1.1	1	1.1	2	1.1
40-49	4	6.1	2	3.0	6	4.6
50-59	6	12.7	8	16.7	14	14.7
60-69	15	35.1	13	26.6	28	30.6
70-79	27	96.0	14	37.2	41	62.4
80-89	13	125.0	12	67.0	25	88.3
90 and over	2	166.6	3	85.7	5	106.3
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**69**	**12.8**	**54**	**9.7**	**123**	**11.2**

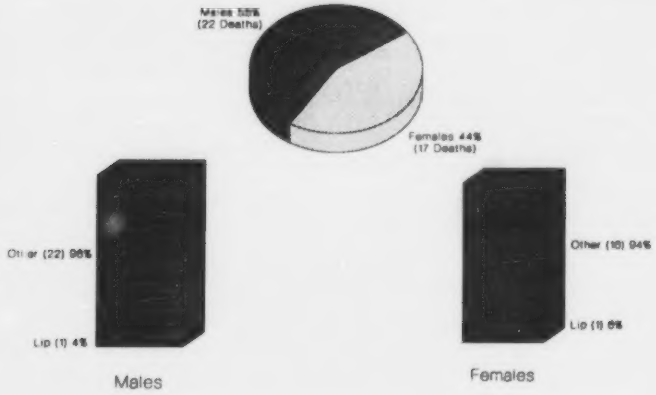
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*1*	*0.3*	*0*	*0.0*	*1*	*0.2*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*4*	*6.1*	*1*	*1.5*	*5*	*3.8*
50-59	*7*	*14.9*	*5*	*10.4*	*12*	*12.6*
60-69	*18*	*42.1*	*16*	*32.8*	*34*	*37.1*
70-79	*23*	*81.8*	*19*	*50.5*	*42*	*63.9*
80-89	*14*	*134.6*	*13*	*72.6*	*27*	*95.4*
90 and over	*2*	*166.6*	*3*	*85.7*	*5*	*106.3*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**69**	**12.8**	**58**	**10.4**	**127**	**11.6**

Buccal Cavity & Pharynx 1990

Incidence



Mortality



1990 TABLE V BUCCAL CAVITY and PHARYNX

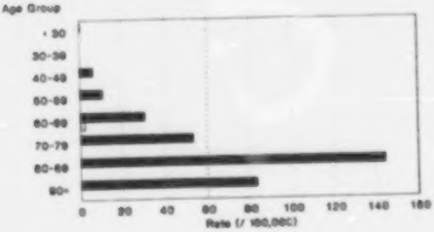
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	3	1.1	1	0.41	4	0.8
30-39	3	3.4	2	2.2	5	2.8
40-49	10	15.3	6	9.1	16	12.2
50-59	25	53.3	7	14.6	32	33.8
60-69	35	81.9	11	22.5	46	50.3
70-79	25	88.9	9	23.9	34	51.7
80-89	23	221.1	3	16.7	26	91.8
90 and over	2	166.6	1	28.5	3	63.8
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**126**	**23.4**	**40**	**7.2**	**166**	**15.2**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*1*	*0.4*	*1*	*0.2*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*1*	*1.5*	*2*	*3.0*	*3*	*2.3*
50-59	*8*	*17.0*	*3*	*6.2*	*11*	*11.6*
60-69	*9*	*21.0*	*4*	*8.2*	*13*	*14.2*
70-79	*3*	*10.6*	*2*	*5.3*	*5*	*7.6*
80-89	*0*	*0.0*	*4*	*22.3*	*4*	*14.1*
90 and over	*1*	*83.3*	*1*	*28.5*	*2*	*42.5*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**22**	**4.0**	**17**	**3.0**	**39**	**3.5**

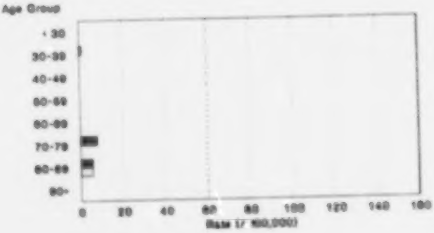
INCIDENCE & MORTALITY 1990

Lip

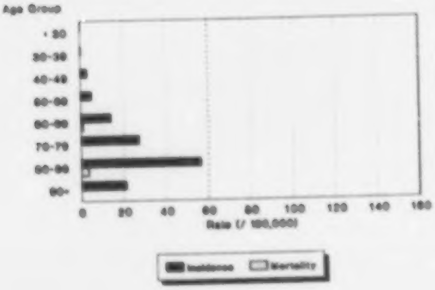
Males



Females



Total Population



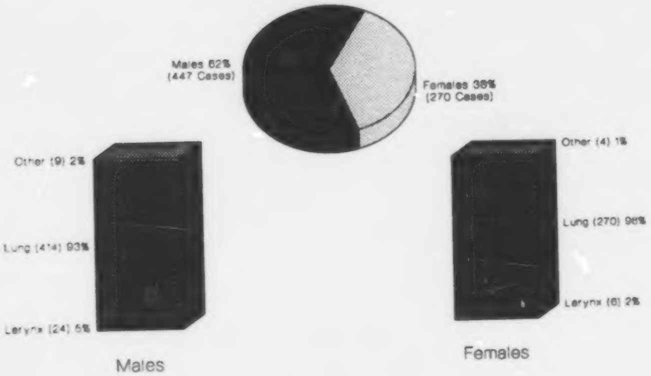
1990 TABLE Va LIP

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	0	0.0	1	0.2
30-39	0	0.0	1	1.1	1	0.5
40-49	4	6.1	0	0.0	4	3.0
50-59	5	10.6	0	0.0	5	5.2
60-69	13	30.4	0	0.0	13	14.2
70-79	15	53.3	3	7.9	18	27.3
80-89	15	144.2	1	5.5	16	56.5
90 and over	1	83.3	0	0.0	1	21.2
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**54**	**10.0**	**5**	**0.9**	**59**	**5.4**

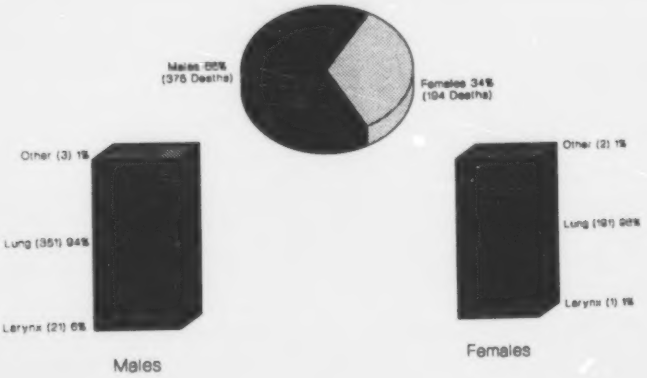
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
60-69	*1*	*2.3*	*0*	*0.0*	*1*	*1.0*
70-79	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
80-89	*0*	*0.0*	*1*	*5.5*	*1*	*3.5*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**1**	**0.1**	**1**	**0.1**	**2**	**0.1**

Respiratory System 1990

Incidence



Mortality



1990 TABLE VI RESPIRATORY SYSTEM

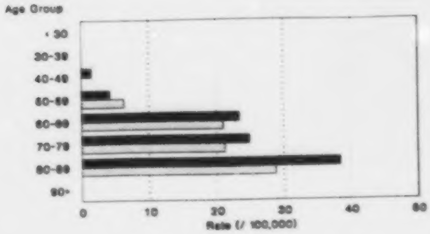
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	0	0.0	1	0.2
30-39	5	5.6	3	3.4	8	4.5
40-49	16	24.5	17	26.0	33	25.3
50-59	52	110.8	40	83.8	92	97.2
60-69	152	355.9	84	172.4	236	258.2
70-79	163	580.0	81	215.4	244	371.3
80-89	53	509.6	43	240.2	96	339.2
90 and over	5	416.6	2	57.1	7	148.9
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**447**	**83.1**	**270**	**48.8**	**717**	**65.7**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*5*	*5.6*	*3*	*3.4*	*8*	*4.5*
40-49	*12*	*18.4*	*6*	*9.1*	*18*	*13.8*
50-59	*42*	*89.5*	*28*	*58.7*	*70*	*73.9*
60-69	*120*	*281.0*	*48*	*98.5*	*168*	*183.8*
70-79	*130*	*462.6*	*65*	*172.8*	*195*	*296.8*
80-89	*61*	*586.5*	*41*	*229.0*	*102*	*360.4*
90 and over	*5*	*416.6*	*3*	*85.7*	*8*	*170.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**375**	**69.7**	**194**	**35.1**	**569**	**52.2**

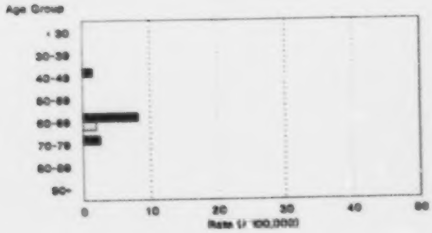
INCIDENCE & MORTALITY 1990

Larynx

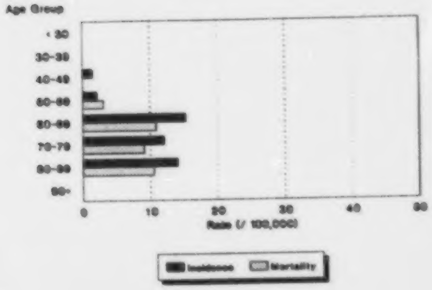
Males



Females



Total Population



1990 TABLE VIa LARYNX

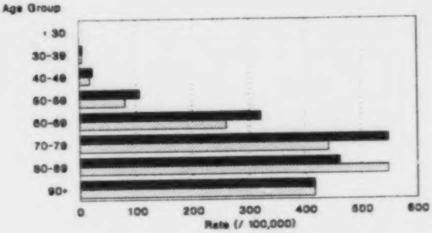
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	0	0.0	0	0.0
30-39	0	0.0	0	0.0	0	0.0
40-49	1	1.5	1	1.5	2	1.5
50-59	2	4.2	0	0.0	2	2.1
60-69	10	23.4	4	8.2	14	15.3
70-79	7	24.9	1	2.6	8	12.1
80-89	4	38.4	0	0.0	4	14.1
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**24**	**4.4**	**6**	**1.0**	**30**	**2.7**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*3*	*6.3*	*0*	*0.0*	*3*	*3.1*
60-69	*9*	*21.0*	*1*	*2.0*	*10*	*10.9*
70-79	*6*	*21.3*	*0*	*0.0*	*6*	*9.1*
80-89	*3*	*28.8*	*0*	*0.0*	*3*	*10.6*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**21**	**3.9**	**1**	**0.1**	**22**	**2.0**

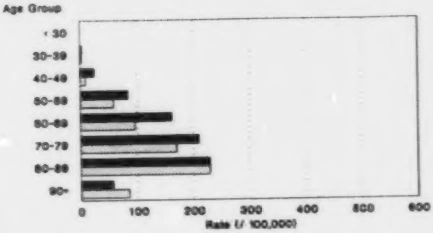
INCIDENCE & MORTALITY 1990

Trachea, Bronchus & Lung

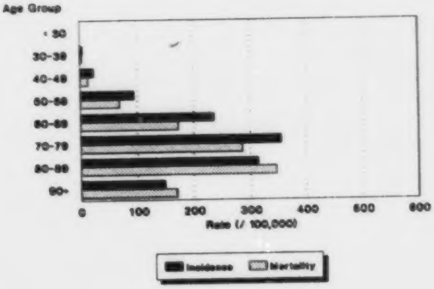
Males



Females



Total Population



1990 TABLE VIb TRACHEA, BRONCHUS and LUNG

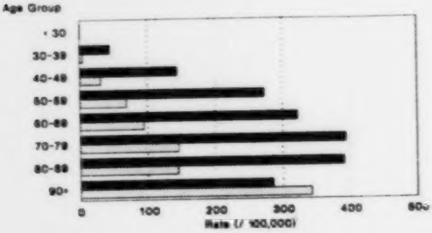
INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	0	0.0	0	0.0	0	0.0
30-39	5	5.6	3	3.4	8	4.5
40-49	15	23.0	16	24.5	31	23.7
50-59	50	106.6	40	83.8	90	95.1
60-69	137	320.8	79	162.2	216	236.3
70-79	154	548.0	79	210.1	233	354.6
80-89	48	461.5	41	229.0	89	314.4
90 and over	5	416.6	2	57.1	7	148.9
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**414**	**77.0**	**260**	**47.0**	**674**	**61.8**

MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*4*	*4.5*	*2*	*2.2*	*6*	*3.4*
40-49	*12*	*18.4*	*6*	*9.1*	*18*	*13.8*
50-59	*38*	*81.0*	*28*	*58.7*	*66*	*69.7*
60-69	*111*	*259.9*	*47*	*96.5*	*158*	*172.8*
70-79	*124*	*441.2*	*64*	*170.2*	*188*	*286.1*
80-89	*57*	*548.0*	*41*	*229.0*	*98*	*346.2*
90 and over	*5*	*416.6*	*3*	*85.7*	*8*	*170.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**351**	**65.3**	**191**	**34.5**	**542**	**49.7**

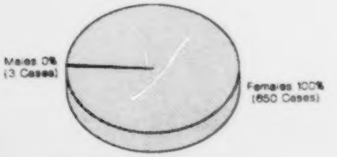
INCIDENCE & MORTALITY 1990

Breast

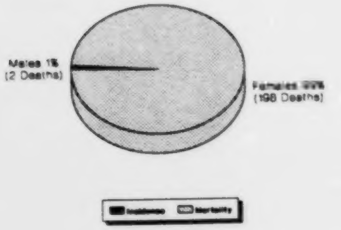
Females



Incidence



Mortality



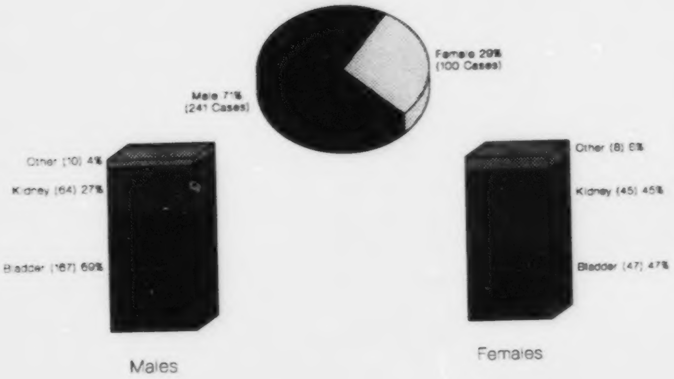
1990 TABLE VII BREAST

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	2	0.8	3	0.6
30-39	0	0.0	39	44.5	39	22.2
40-49	0	0.0	94	143.9	94	72.0
50-59	1	2.1	130	272.5	131	138.4
60-69	0	0.0	157	322.3	157	171.7
70-79	1	3.5	148	393.6	149	226.7
80-89	0	0.0	70	391.0	70	247.3
90 and over	0	0.0	10	285.7	10	212.7
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**3**	**0.5**	**650**	**117.6**	**653**	**59.9**

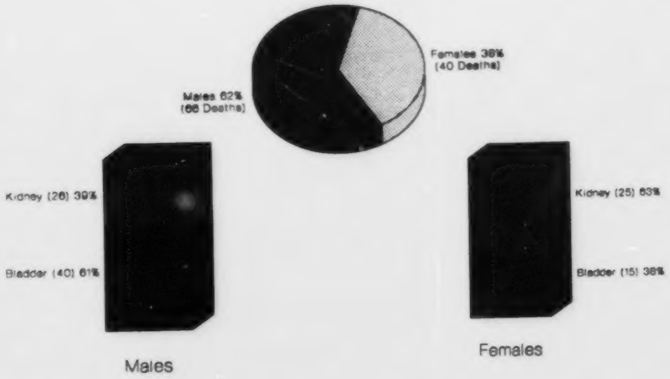
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*2*	*0.8*	*2*	*0.4*
30-39	*0*	*0.0*	*4*	*4.5*	*4*	*2.2*
40-49	*0*	*0.0*	*20*	*30.6*	*20*	*15.3*
50-59	*0*	*0.0*	*33*	*69.1*	*33*	*34.8*
60-69	*1*	*2.3*	*46*	*94.4*	*47*	*51.4*
70-79	*1*	*3.5*	*55*	*146.2*	*56*	*85.2*
80-89	*0*	*0.0*	*26*	*145.2*	*26*	*91.8*
90 and over	*0*	*0.0*	*12*	*342.8*	*12*	*255.3*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**2**	**0.3**	**198**	**35.8**	**200**	**18.3**

Urinary Tract 1990

Incidence



Mortality



1990 TABLE VIII URINARY TRACT

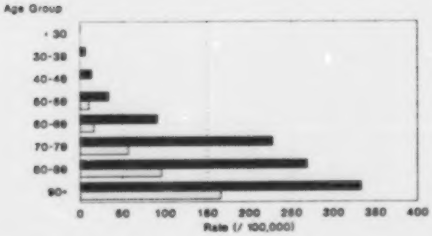
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	2	0.8	3	0.6
30-39	8	9.1	4	4.5	12	6.8
40-49	10	15.3	10	15.3	20	15.3
50-59	33	70.3	15	31.4	48	50.7
60-69	57	133.4	17	34.9	74	80.9
70-79	94	334.5	27	71.8	121	184.1
80-89	34	326.9	19	106.1	53	187.2
90 and over	4	333.3	6	171.4	10	212.7
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**241**	**44.8**	**100**	**18.0**	**341**	**31.2**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*0*	*0.0*	*3*	*4.5*	*3*	*2.3*
50-59	*10*	*21.3*	*4*	*8.3*	*14*	*14.7*
60-69	*17*	*39.8*	*4*	*8.2*	*21*	*22.9*
70-79	*23*	*81.8*	*16*	*42.5*	*39*	*59.3*
80-89	*14*	*134.6*	*9*	*50.2*	*23*	*81.2*
90 and over	*2*	*166.6*	*3*	*85.7*	*5*	*106.3*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**66**	**12.2**	**40**	**7.2**	**106**	**9.7**

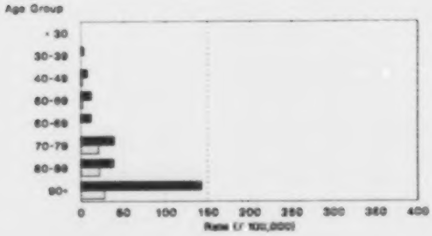
INCIDENCE & MORTALITY 1990

Bladder

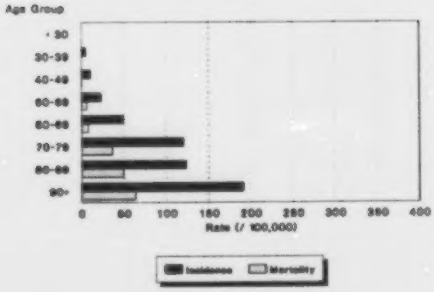
Males



Females



Total Population



1990 TABLE VIIIa BLADDER

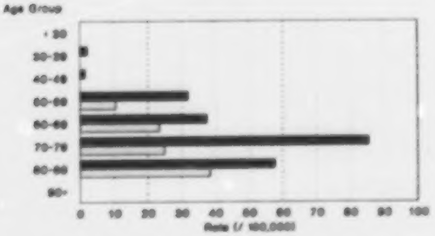
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	1	0.3	0	0.0	1	0.2
30-39	6	6.8	3	3.4	9	5.1
40-49	9	13.8	5	7.6	14	10.7
50-59	16	34.1	6	12.5	22	23.2
60-69	39	91.3	6	12.3	45	49.2
70-79	64	227.7	15	39.8	79	120.2
80-89	28	269.2	7	39.1	35	123.6
90 and over	4	333.3	5	142.8	9	191.4
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**167**	**31.0**	**47**	**8.5**	**214**	**19.6**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*1*	*1.5*	*1*	*0.7*
50-59	*5*	*10.6*	*1*	*2.0*	*6*	*6.3*
60-69	*7*	*16.3*	*0*	*0.0*	*7*	*7.6*
70-79	*16*	*56.9*	*8*	*21.2*	*24*	*36.5*
80-89	*10*	*96.1*	*4*	*22.3*	*14*	*49.4*
90 and over	*2*	*166.6*	*1*	*28.5*	*3*	*63.8*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**40**	**7.4**	**15**	**2.7**	**55**	**5.0**

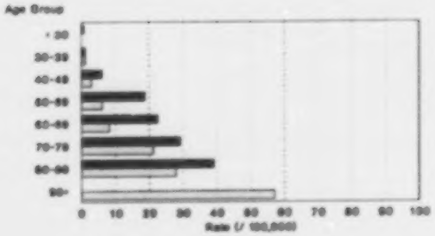
INCIDENCE & MORTALITY 1990

Kidney

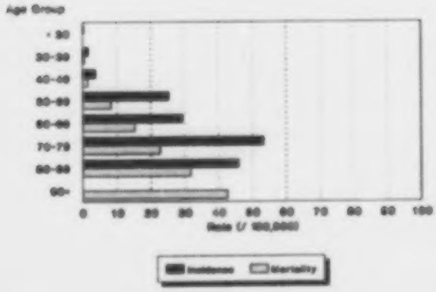
Males



Females



Total Population



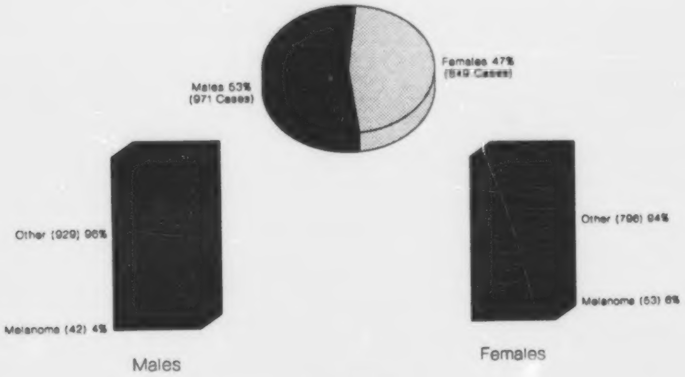
1990 TABLE VIIIb KIDNEY

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	2	0.8	2	0.4
30-39	2	2.2	1	1.1	3	1.7
40-49	1	1.5	4	6.1	5	3.8
50-59	15	31.9	9	18.8	24	25.3
60-69	16	37.4	11	22.5	27	29.5
70-79	24	85.4	11	29.2	35	53.2
80-89	6	57.6	7	39.1	13	45.9
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**64**	**11.9**	**45**	**8.1**	**109**	**10.0**

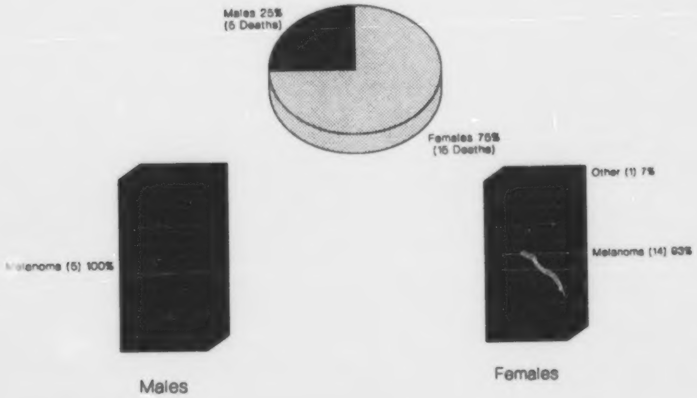
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*0*	*0.0*	*2*	*3.0*	*2*	*1.5*
50-59	*5*	*10.6*	*3*	*6.2*	*8*	*8.4*
60-69	*10*	*23.4*	*4*	*8.2*	*14*	*15.3*
70-79	*7*	*24.9*	*8*	*21.2*	*15*	*22.8*
80-89	*4*	*38.4*	*5*	*27.9*	*9*	*31.8*
90 and over	*0*	*0.0*	*2*	*57.1*	*2*	*42.5*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**26**	**4.8**	**25**	**4.5**	**51**	**4.6**

Skin 1990

Incidence



Mortality



1990 TABLE IX SKIN

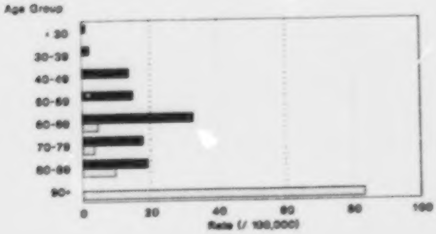
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	11	4.3	12	4.9	23	4.6
30-39	29	32.9	52	59.3	81	46.1
40-49	84	129.0	66	101.0	150	115.0
50-59	109	232.4	99	207.5	208	219.8
60-69	273	639.3	188	386.0	461	504.3
70-79	280	996.4	238	632.9	518	788.4
80-89	159	1,528.8	157	877.0	316	1,116.6
90 and over	26	2,166.6	36	1,028.5	62	1,319.1
Age not stated	0	0.0	1	0.0	1	0.0
TOTAL	**971**	**180.6**	**849**	**153.6**	**1,820**	**167.0**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*1*	*0.4*	*1*	*0.2*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*0*	*0.0*	*2*	*3.0*	*2*	*1.5*
50-59	*0*	*0.0*	*3*	*6.2*	*3*	*3.1*
60-69	*2*	*4.6*	*4*	*8.2*	*6*	*6.5*
70-79	*1*	*3.5*	*1*	*2.6*	*2*	*3.0*
80-89	*1*	*9.6*	*2*	*11.1*	*3*	*10.6*
90 and over	*1*	*83.3*	*1*	*28.5*	*2*	*42.5*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**5**	**0.9**	**15**	**2.7**	**20**	**1.8**

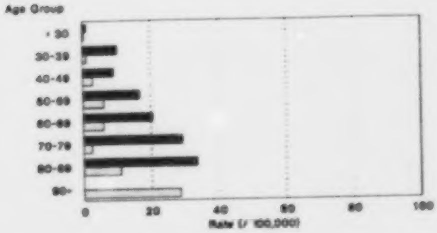
INCIDENCE & MORTALITY 1990

Melanoma

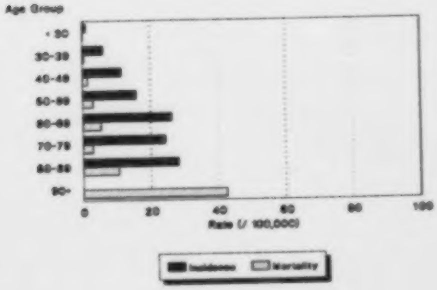
Males



Females



Total Population



1990 TABLE IXa MELANOMA

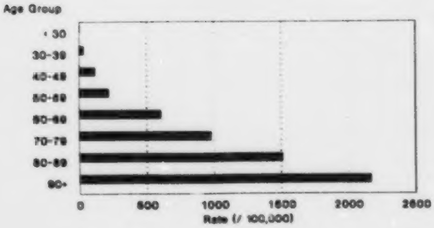
INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	3	1.1	3	1.2	6	1.2
30-39	2	2.2	9	10.2	11	6.2
40-49	9	13.8	6	9.1	15	11.5
50-59	7	14.9	8	16.7	15	15.8
60-69	14	32.7	10	20.5	24	26.2
70-79	5	17.7	11	29.2	16	24.3
80-89	2	19.2	6	33.5	8	28.2
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**42**	**7.8**	**53**	**9.5**	**95**	**8.7**

MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*1*	*0.4*	*1*	*0.2*
30-39	*0*	*0.0*	*1*	*1.1*	*1*	*0.5*
40-49	*0*	*0.0*	*2*	*3.0*	*2*	*1.5*
50-59	*0*	*0.0*	*3*	*6.2*	*3*	*3.1*
60-69	*2*	*4.6*	*3*	*6.1*	*5*	*5.4*
70-79	*1*	*3.5*	*1*	*2.6*	*2*	*3.0*
80-89	*1*	*9.6*	*2*	*11.1*	*3*	*10.6*
90 and over	*1*	*83.3*	*1*	*28.5*	*2*	*42.5*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**5**	**0.9**	**14**	**2.5**	**19**	**1.7**

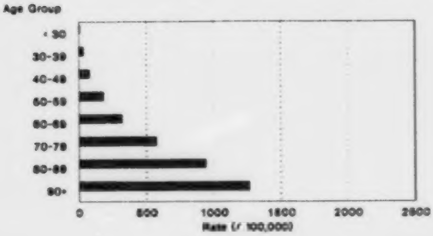
INCIDENCE & MORTALITY 1990

Other Malignant Neoplasms
Skin

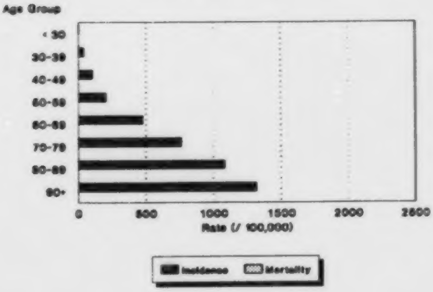
Males



Females



Total Population



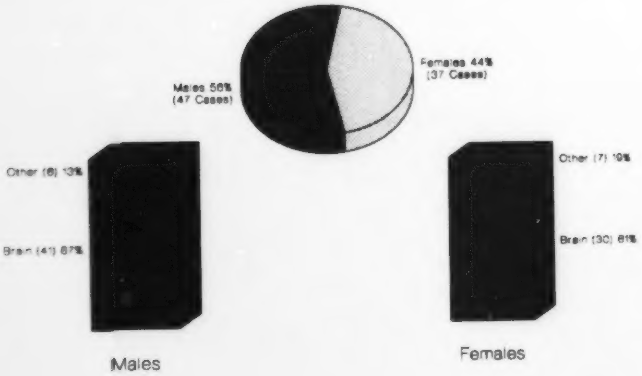
1990 TABLE IXb OTHER MALIGNANT NEOPLASMS (SKIN)

INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	7	2.7	9	3.6	16	3.2
30-39	27	30.7	43	49.0	70	39.8
40-49	75	115.2	60	91.8	135	103.5
50-59	102	217.4	91	190.7	193	204.0
60-69	258	604.2	176	361.3	434	474.8
70-79	275	978.6	226	601.0	501	762.5
80-89	157	1,509.6	150	837.9	307	1,084.8
90 and over	26	2,166.6	36	1,028.5	62	1,319.1
Age not stated	0	0.0	1	0.0	1	0.0
TOTAL	**927**	**172.4**	**792**	**143.3**	**1,719**	**157.7**

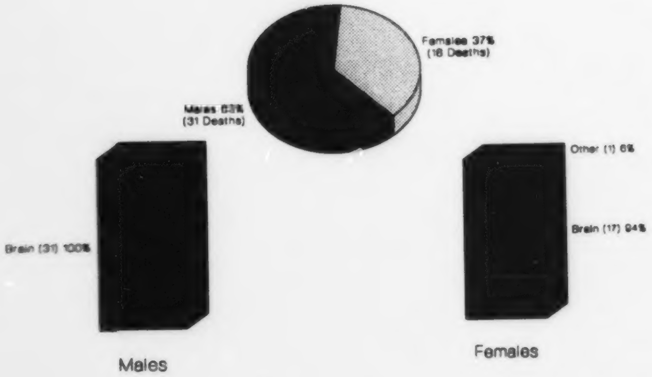
MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
60-69	*0*	*0.0*	*1*	*2.0*	*1*	*1.0*
70-79	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
80-89	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**0**	**0.0**	**1**	**0.1**	**1**	**0.0**

Brain & Nervous System 1990

Incidence



Mortality



1990 TABLE X BRAIN and NERVOUS SYSTEM

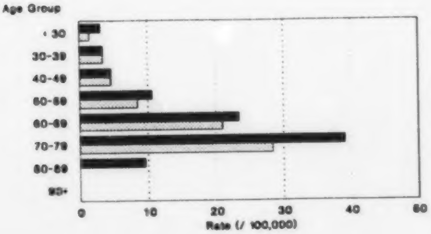
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	9	3.5	6	2.4	15	3.0
30-39	4	4.5	5	5.7	9	5.1
40-49	4	6.1	1	1.5	5	3.8
50-59	6	12.7	3	6.2	9	9.5
60-69	11	25.7	9	18.4	20	21.8
70-79	12	42.7	6	15.9	18	27.3
80-89	1	9.6	5	27.9	6	21.2
90 and over	0	0.0	2	57.1	2	42.5
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**47**	**8.7**	**37**	**6.6**	**84**	**7.7**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*4*	*1.5*	*0*	*0.0*	*4*	*0.8*
30-39	*3*	*3.4*	*0*	*0.0*	*3*	*1.7*
40-49	*3*	*4.6*	*3*	*4.5*	*6*	*4.6*
50-59	*4*	*8.5*	*4*	*8.3*	*8*	*8.4*
60-69	*9*	*21.0*	*4*	*8.2*	*13*	*14.2*
70-79	*8*	*28.4*	*4*	*10.6*	*12*	*18.2*
80-89	*0*	*0.0*	*2*	*11.1*	*2*	*7.0*
90 and over	*0*	*0.0*	*1*	*28.5*	*1*	*21.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**31**	**5.7**	**18**	**3.2**	**49**	**4.4**

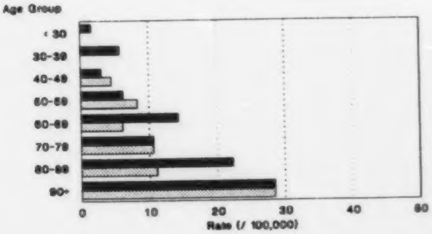
INCIDENCE & MORTALITY 1990

Brain

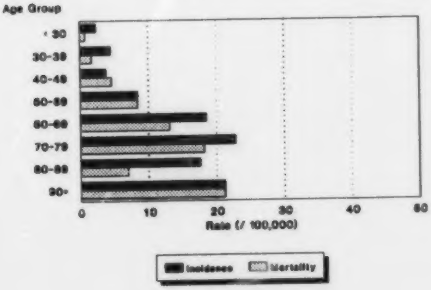
Males



Females



Total Population



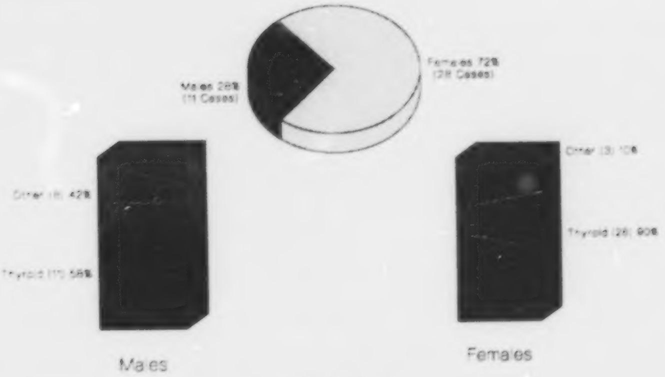
1990 TABLE Xa BRAIN

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	8	3.1	4	1.6	12	2.4
30-39	3	3.4	5	5.7	8	4.5
40-49	3	4.6	2	3.0	5	3.8
50-59	5	10.6	3	6.2	8	8.4
60-69	10	23.4	7	14.3	17	18.5
70-79	11	39.1	4	10.6	15	22.8
80-89	1	9.6	4	22.3	5	17.6
90 and over	0	0.0	1	28.5	1	21.2
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**41**	**7.6**	**30**	**5.4**	**71**	**6.5**

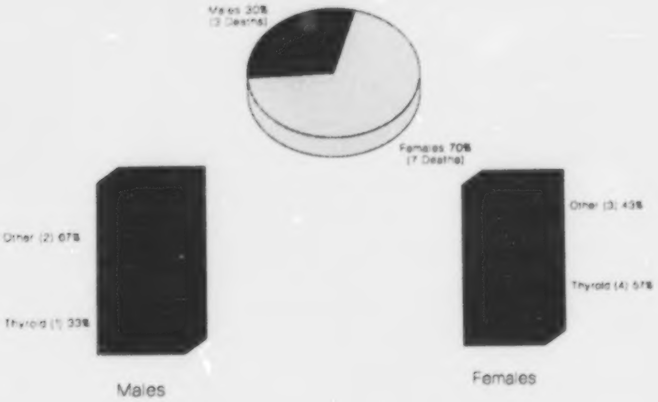
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*4*	*1.5*	*0*	*0.0*	*4*	*0.8*
30-39	*3*	*3.4*	*0*	*0.0*	*3*	*1.7*
40-49	*3*	*4.6*	*3*	*4.5*	*6*	*4.6*
50-59	*4*	*8.5*	*4*	*8.3*	*8*	*8.4*
60-69	*9*	*21.0*	*3*	*6.1*	*12*	*13.1*
70-79	*8*	*28.4*	*4*	*10.6*	*12*	*18.2*
80-89	*0*	*0.0*	*2*	*11.1*	*2*	*7.0*
90 and over	*0*	*0.0*	*1*	*28.5*	*1*	*21.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**31**	**5.7**	**17**	**3.0**	**48**	**4.4**

Thyroid & Endocrine Glands 1990

Incidence



Mortality



1990 TABLE XI THYROID and ENDOCRINE GLANDS

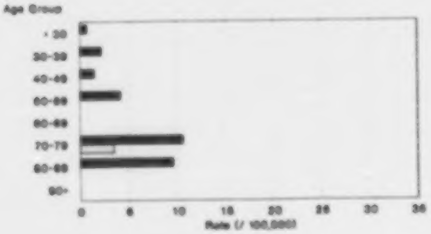
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	4	1.5	11	4.5	15	3.0
30-39	2	2.2	9	10.2	11	6.2
40-49	2	3.0	2	3.0	4	3.0
50-59	4	8.5	2	4.1	6	6.3
60-69	1	2.3	4	8.2	5	5.4
70-79	5	17.7	2	5.3	7	10.6
80-89	1	9.6	1	5.5	2	7.0
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**19**	**3.5**	**31**	**5.6**	**50**	**4.5**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*1*	*0.3*	*0*	*0.0*	*1*	*0.2*
30-39	*1*	*1.1*	*0*	*0.0*	*1*	*0.5*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*0*	*0.0*	*C*	*0.0*	*0*	*0.0*
60-69	*0*	*0.0*	*1*	*2.0*	*1*	*1.0*
70-79	*1*	*3.5*	*2*	*5.3*	*3*	*4.5*
80-89	*0*	*0.0*	*3*	*16.7*	*3*	*10.6*
90 and over	*0*	*0.0*	*1*	*28.5*	*1*	*21.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**3**	**0.5**	**7**	**1.2**	**10**	**0.9**

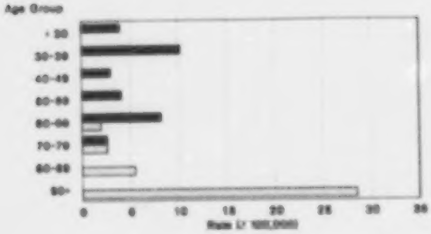
INCIDENCE & MORTALITY 1990

Thyroid

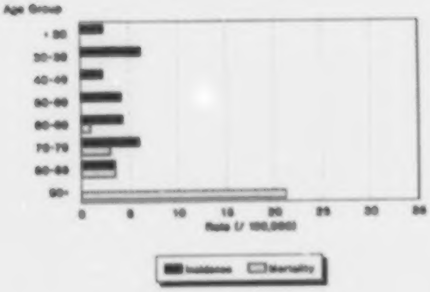
Males



Females



Total Population



1990 TABLE XIa THYROID

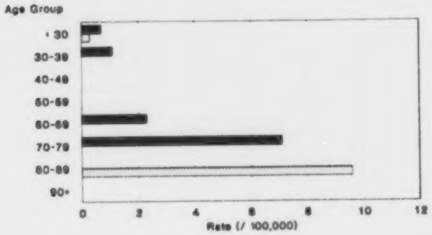
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	2	0.7	10	4.0	12	2.4
30-39	2	2.2	9	10.2	11	6.2
40-49	1	1.5	2	3.0	3	2.3
50-59	2	4.2	2	4.1	4	4.2
60-69	0	0.0	4	8.2	4	4.3
70-79	3	10.6	1	2.6	4	6.0
80-89	1	9.6	0	0.0	1	3.5
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	11	2.0	28	5.0	39	3.5

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
60-69	*0*	*0.0*	*1*	*2.0*	*1*	*1.0*
70-79	*1*	*3.5*	*1*	*2.6*	*2*	*3.0*
80-89	*0*	*0.0*	*1*	*5.5*	*1*	*3.5*
90 and over	*0*	*0.0*	*1*	*28.5*	*1*	*21.2*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	1	0.1	4	0.7	5	0.4

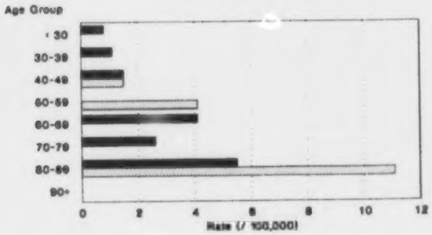
INCIDENCE & MORTALITY 1990

Bone

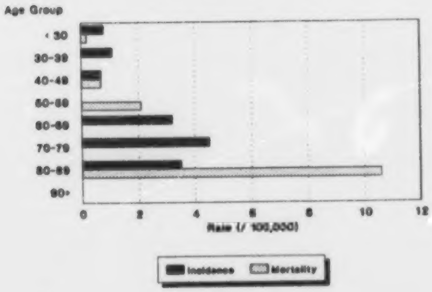
Males



Females



Total Population



1990 TABLE XII BONE

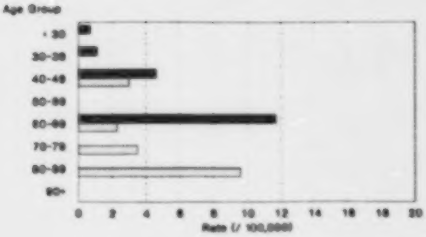
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	2	0.7	2	0.8	4	0.8
30-39	1	1.1	1	1.1	2	1.1
40-49	0	0.0	1	1.5	1	0.7
50-59	0	0.0	0	0.0	0	0.0
60-69	1	2.3	2	4.1	3	3.2
70-79	2	7.1	1	2.6	3	4.5
80-89	0	0.0	1	5.5	1	3.5
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**6**	**1.1**	**8**	**1.4**	**14**	**1.2**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*1*	*0.3*	*0*	*0.0*	*1*	*0.2*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*0*	*0.0*	*1*	*1.5*	*1*	*0.7*
50-59	*0*	*0.0*	*2*	*4.1*	*2*	*2.1*
60-69	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
70-79	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
80-89	*1*	*9.6*	*2*	*11.1*	*3*	*10.6*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**2**	**0.3**	**5**	**0.9**	**7**	**0.6**

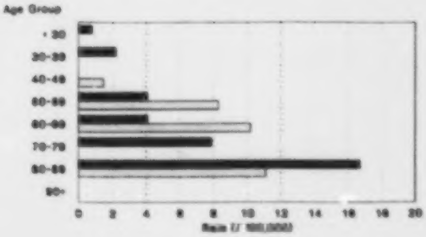
INCIDENCE & MORTALITY 1990

Connective Tissue

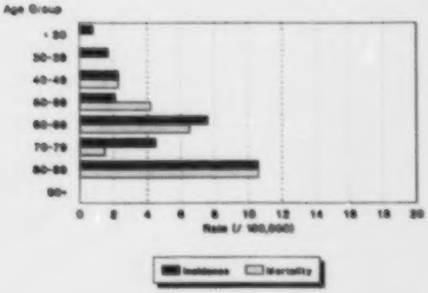
Males



Females



Total Population



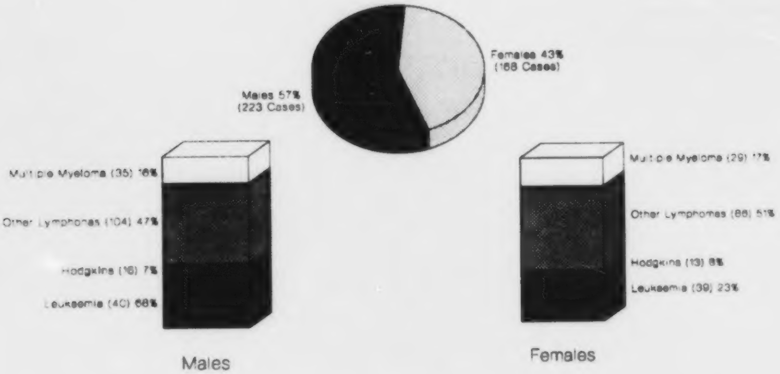
1990 TABLE XIII CONNECTIVE TISSUE

INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	2	0.7	2	0.8	4	0.8
30-39	1	1.1	2	2.2	3	1.7
40-49	3	4.6	0	0.0	3	2.3
50-59	0	0.0	2	4.1	2	2.1
60-69	5	11.7	2	4.1	7	7.6
70-79	0	0.0	3	7.9	3	4.5
80-89	0	0.0	3	16.7	3	10.6
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	11	2.0	14	2.5	25	2.2

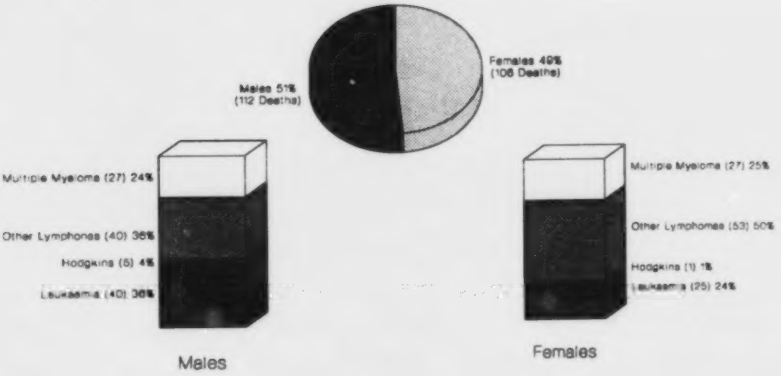
MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*2*	*3.0*	*1*	*1.5*	*3*	*2.3*
50-59	*0*	*0.0*	*4*	*8.3*	*4*	*4.2*
60-69	*1*	*2.3*	*5*	*10.2*	*6*	*6.5*
70-79	*1*	*3.5*	*0*	*0.0*	*1*	*1.5*
80-89	*1*	*9.6*	*2*	*11.1*	*3*	*10.6*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	5	0.9	12	2.1	17	1.5

Lymphatic & Haematopoietic Systems 1990

Incidence



Mortality



1990 TABLE XIV LYMPHATIC & HAEMATOPOIETIC SYSTEMS

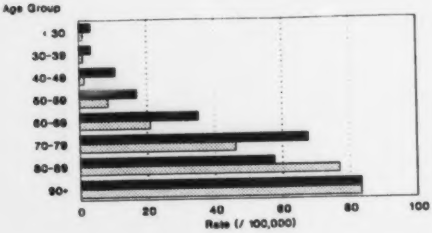
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	19	7.4	14	5.7	33	6.6
30-39	10	11.3	6	6.8	16	9.1
40-49	18	27.6	9	13.7	27	20.7
50-59	38	81.0	20	41.9	58	61.3
60-69	51	119.4	33	67.7	84	91.9
70-79	56	199.2	52	138.2	108	164.3
80-89	26	250.0	31	173.1	57	201.4
90 and over	5	416.6	3	85.7	8	170.2
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**223**	**41.4**	**168**	**30.4**	**391**	**35.8**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*5*	*1.9*	*4*	*1.6*	*9*	*1.8*
30-39	*2*	*2.2*	*1*	*1.1*	*3*	*1.7*
40-49	*4*	*6.1*	*3*	*4.5*	*7*	*5.3*
50-59	*16*	*34.1*	*6*	*12.5*	*22*	*23.2*
60-69	*22*	*51.5*	*21*	*43.1*	*43*	*47.0*
70-79	*35*	*124.5*	*33*	*87.7*	*68*	*103.5*
80-89	*24*	*230.7*	*31*	*173.1*	*55*	*194.3*
90 and over	*4*	*333.3*	*7*	*200.0*	*11*	*234.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**112**	**20.8**	**106**	**19.1**	**218**	**20.0**

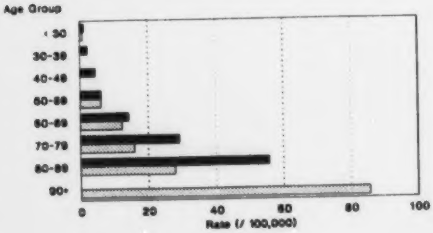
INCIDENCE & MORTALITY 1990

Leukaemia

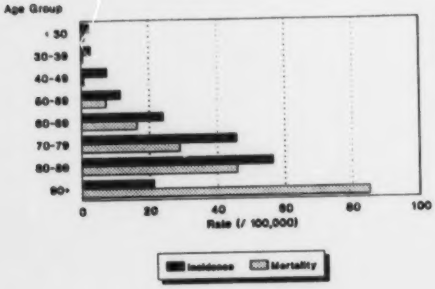
Males



Females



Total Population



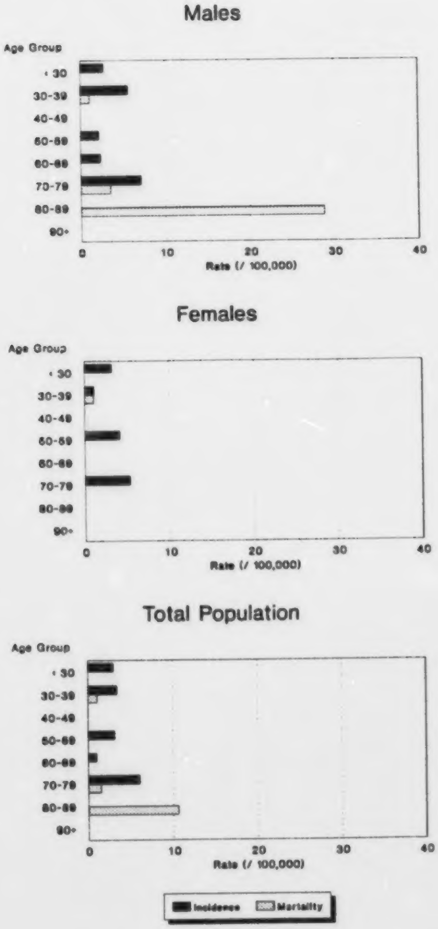
1990 TABLE XIVa LEUKAEMIA

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	9	3.5	3	1.2	12	2.4
30-39	3	3.4	2	2.2	5	2.8
40-49	7	10.7	3	4.5	10	7.6
50-59	8	17.0	3	6.2	11	11.6
60-69	15	35.1	7	14.3	22	24.0
70-79	19	67.6	11	29.2	30	45.6
80-89	6	57.6	10	55.8	16	56.5
90 and over	1	83.3	0	0.0	1	21.2
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**68**	**12.6**	**39**	**7.0**	**107**	**9.8**

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	3	1.1	2	0.8	5	1.0
30-39	1	1.1	0	0.0	1	0.5
40-49	1	1.5	0	0.0	1	0.7
50-59	4	8.5	3	6.2	7	7.3
60-69	9	21.0	6	12.3	15	16.4
70-79	13	46.2	6	15.9	19	28.9
80-89	8	76.9	5	27.9	13	45.9
90 and over	1	83.3	3	85.7	4	85.1
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**40**	**7.4**	**25**	**4.5**	**65**	**5.9**

INCIDENCE & MORTALITY 1990

Hodgkins Disease



Males

Females

Total Population

1990 TABLE XIVb HODGKINS DISEASE

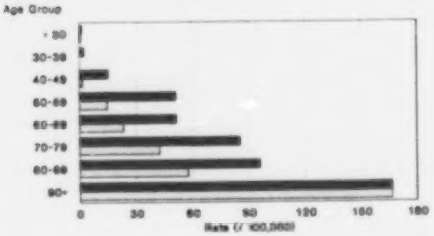
INCIDENCE	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	7	2.7	8	3.2	15	3.0
30-39	5	5.6	1	1.1	6	3.4
40-49	0	0.0	0	0.0	0	0.0
50-59	1	2.1	2	4.1	3	3.1
60-69	1	2.3	0	0.0	1	1.0
70-79	2	7.1	2	5.3	4	6.0
80-89	0	0.0	0	0.0	0	0.0
90 and over	0	0.0	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	**16**	**2.9**	**13**	**2.3**	**29**	**2.6**

MORTALITY	**Male**	**Rate**	**Female**	**Rate**	**TOTAL**	**RATE**
Under 30	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
30-39	*1*	*1.1*	*1*	*1.1*	*2*	*1.1*
40-49	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
50-59	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
60-69	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
70-79	*1*	*3.5*	*0*	*0.0*	*1*	*1.5*
80-89	*3*	*28.8*	*0*	*0.0*	*3*	*10.6*
90 and over	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	**5**	**0.9**	**1**	**0.1**	**6**	**0.5**

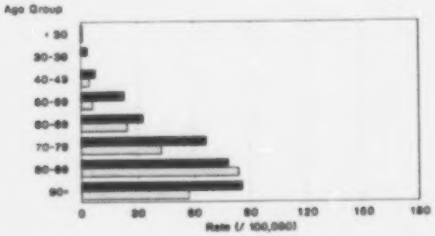
INCIDENCE & MORTALITY 1990

Lymphomas

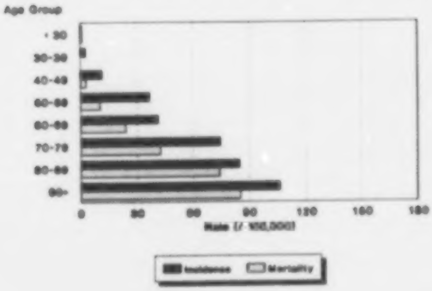
Males



Females



Total Population



1990 TABLE XIVc LYMPHOMAS

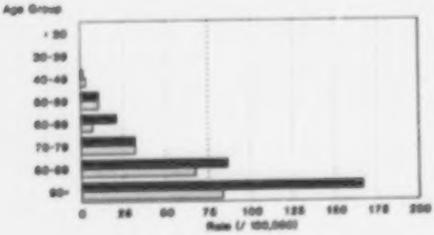
INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	3	1.1	2	0.8	5	1.0
30-39	2	2.2	3	3.4	5	2.8
40-49	10	15.3	5	7.6	15	11.5
50-59	24	51.1	11	23.0	35	36.9
60-69	22	51.5	16	32.8	38	41.5
70-79	24	85.4	25	66.4	49	74.5
80-89	10	96.1	14	78.2	24	84.8
90 and over	2	166.6	3	85.7	5	106.3
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	97	18.0	79	14.3	176	16.1

MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	*2*	*0.7*	*2*	*0.8*	*4*	*0.8*
30-39	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
40-49	*1*	*1.5*	*3*	*4.5*	*4*	*3.0*
50-59	*7*	*14.9*	*3*	*6.2*	*10*	*10.5*
60-69	*10*	*23.4*	*12*	*24.6*	*22*	*24.0*
70-79	*12*	*42.7*	*16*	*42.5*	*28*	*42.6*
80-89	*6*	*57.6*	*15*	*83.7*	*21*	*74.2*
90 and over	*2*	*166.6*	*2*	*57.1*	*4*	*85.1*
Age not stated	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
TOTAL	40	7.4	53	9.5	93	8.5

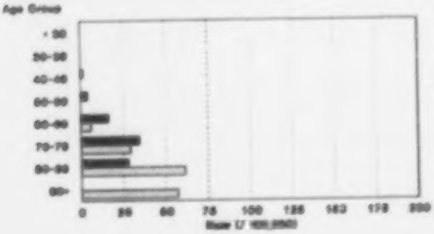
INCIDENCE & MORTALITY 1990

Multiple Myeloma

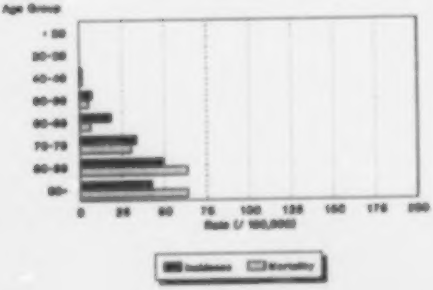
Males



Females



Total Population



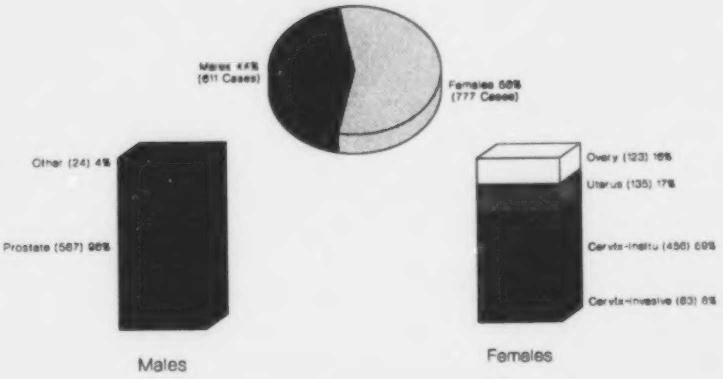
1990 TABLE XIVd MULTIPLE MYELOMA

INCIDENCE	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	0	0.0	0	0.0
30-39	0	0.0	0	0.0	0	0.0
40-49	1	1.5	1	1.5	2	1.5
50-59	5	10.6	2	4.1	7	7.3
60-69	9	21.0	8	16.4	17	18.5
70-79	9	32.0	13	34.5	22	33.4
80-89	9	86.5	5	27.9	14	49.4
90 and over	2	166.6	0	0.0	2	42.5
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	35	6.5	29	5.2	64	5.8

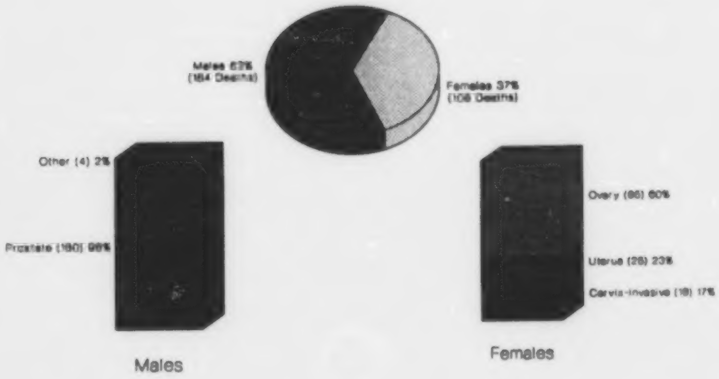
MORTALITY	Male	Rate	Female	Rate	TOTAL	RATE
Under 30	0	0.0	0	0.0	0	0.0
30-39	0	0.0	0	0.0	0	0.0
40-49	2	3.0	0	0.0	2	1.5
50-59	5	10.6	0	0.0	5	5.2
60-69	3	7.0	3	6.1	6	6.5
70-79	9	32.0	11	29.2	20	30.4
80-89	7	67.3	11	61.4	18	63.6
90 and over	1	83.3	2	57.1	3	63.8
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	27	5.0	27	4.8	54	4.9

Genital Organs 1990

Incidence



Mortality



1990 TABLE XVa FEMALE GENITAL ORGANS

INCIDENCE	All Organs		Cervix Uteri			
			Insitu		Invasive*	
	N	Rate	N	Rate	N	Rate
Under 30	223	91.3	209	85.6	3	1.2
30-39	208	237.4	167	190.6	23	26.3
40-49	100	153.1	53	81.2	8	12.3
50-59	69	144.6	13	27.3	10	20.9
60-69	83	170.4	9	18.5	7	14.4
70-79	68	180.8	5	13.3	10	26.6
80-89	22	122.9	0	0.0	2	11.2
90 an over	4	114.2	0	0.0	0	0.0
Age not stated	0	0.0	0	0.0	0	0.0
TOTAL	777	140.6	456	82.5	63	11.4

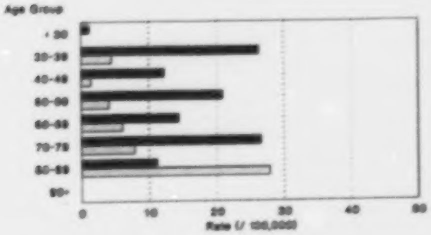
* these include 8 Micro-Invasive cases

MORTALITY	All Organs		Cervix Uteri			
			Insitu		Invasive	
	N	Rate	N	Rate	N	Rate
Under 30	*2*	*0.8*	-	-	*0*	*0.0*
30-39	*4*	*4.5*	-	-	*4*	*4.5*
40-49	*4*	*6.1*	-	-	*1*	*1.5*
50-59	*13*	*27.2*	-	-	*2*	*4.1*
60-69	*22*	*45.1*	-	-	*3*	*6.1*
70-79	*32*	*85.1*	-	-	*3*	*7.9*
80-89	*27*	*150.8*	-	-	*5*	*27.9*
90 and over	*4*	*114.2*	-	-	*0*	*0.0*
Age not stated	*0*	*0.0*	-	-	*0*	*0.0*
TOTAL	108	19.5	-	-	18	3.2

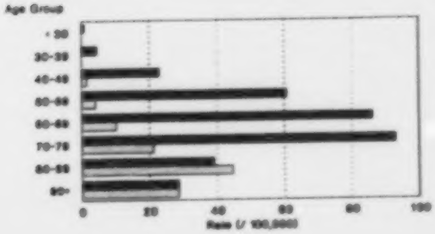
INCIDENCE & MORTALITY 1990

Female Genital Organs

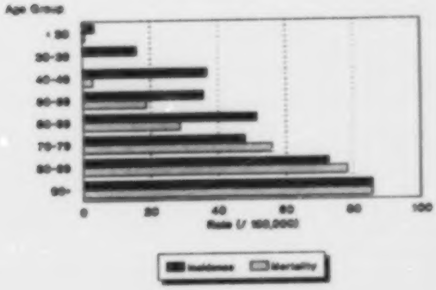
Cervix - Invasive



Uterus



Ovary



1990 TABLE XVb FEMALE GENITAL ORGANS

INCIDENCE

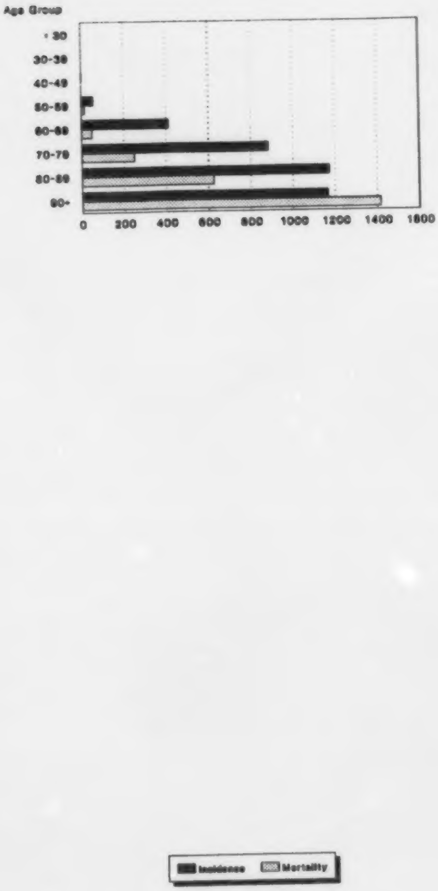
	Uterus-Corpus Etc. (Except Cervix)			Ovaries,Fallopian-Tubes,Broad Ligaments & Other Genital Organs	
	N	Rate		N	Rate
Under 30	2	0.8	Under 30	9	3.6
30-39	4	4.5	30-39	14	15.9
40-49	15	22.9	40-49	24	36.7
50-59	29	60.7	50-59	17	35.6
60-69	42	86.2	60-69	25	51.3
70-79	35	93.0	70-79	18	47.8
80-89	7	39.1	80-89	13	72.6
90 and over	1	28.5	90 and over	3	85.7
Age not stated	0	0.0	Age not stated	0	0.0
TOTAL	135	24.4	**TOTAL**	123	22.2

MORTALITY

	Uterus-Corpus Etc. (Except Cervix)			Ovaries,Fallopian-Tubes,Broad Ligaments & Other Genital Organs	
	N	Rate		N	Rate
Under 30	*0*	*0.0*	*Under 30*	*2*	*0.8*
30-39	*0*	*0.0*	*30-39*	*0*	*0.0*
40-49	*1*	*1.5*	*40-49*	*2*	*3.0*
50-59	*2*	*4.1*	*50-59*	*9*	*18.8*
60-69	*5*	*10.2*	*60-69*	*14*	*28.7*
70-79	*8*	*21.2*	*70-79*	*21*	*55.8*
80-89	*8*	*44.6*	*80-89*	*14*	*78.2*
90 and over	*1*	*28.5*	*90 and over*	*3*	*85.7*
Age not stated	*0*	*0.0*	*Age not stated*	*0*	*0.0*
TOTAL	25	4.5	**TOTAL**	65	11.7

INCIDENCE & MORTALITY 1990

Prostate



1990 TABLE XVIa MALE GENITAL ORGANS

INCIDENCE

All Organs	N	Rate	Prostate	N	Rate
Under 30	6	2.3	Under 30	0	0.0
30-39	9	10.2	30-39	0	0.0
40-49	3	4.6	40-49	1	1.5
50-59	26	55.4	50-59	26	55.4
60-69	177	414.5	60-69	176	412.1
70-79	253	900.3	70-79	248	882.5
80-89	123	1,182.6	80-89	122	1,173.0
90 and over	14	1,166.6	90 and over	14	1,166.6
Age not stated	0	0.0	Age not stated	0	0.0
TOTAL	**611**	**113.6**	**TOTAL**	**587**	**109.2**

MORTALITY

All Organs	N	Rate	Prostate	N	Rate
Under 30	*0*	*0.0*	*Under 30*	*0*	*0.0*
30-39	*1*	*1.1*	*30-39*	*0*	*0.0*
40-49	*0*	*0.0*	*40-49*	*0*	*0.0*
50-59	*7*	*14.9*	*50-59*	*7*	*14.9*
60-69	*24*	*56.2*	*60-69*	*21*	*49.1*
70-79	*70*	*249.1*	*70-79*	*70*	*249.1*
80-89	*65*	*625.0*	*80-89*	*65*	*625.0*
90 and over	*17*	*1,416.6*	*90 and over*	*17*	*1,416.6*
Age not stated	*0*	*0.0*	*Age not stated*	*0*	*0.0*
TOTAL	**184**	**34.2**	**TOTAL**	**180**	**33.4**

1990 TABLE XVIb MALE GENITAL ORGANS

INCIDENCE			MORTALITY		
Other Genital Organs	N	Rate	Other Genital Organs	N	Rate
Under 30	6	2.3	*Under 30*	*0*	*0.0*
30-39	9	10.2	*30-39*	*1*	*1.1*
40-49	2	3.0	*40-49*	*0*	*0.0*
50-59	0	0.0	*50-59*	*0*	*0.0*
60-69	1	2.3	*60-69*	*3*	*7.0*
70-79	5	17.7	*70-79*	*0*	*0.0*
80-89	1	9.6	*80-89*	*0*	*0.0*
90 and over	0	0.0	*90 and over*	*0*	*0.0*
Age not stated	0	0.0	*Age not stated*	*0*	*0.0*
TOTAL	**24**	**4.4**	**TOTAL**	**4**	**0.7**

1990 TABLE XVIIa CANCER INCIDENCE - BY SITE*

ICDA 9th Rev.	Site	Male	Female	Total
140	Lip	51	3	54
141	Tongue	13	10	23
142	Salivary Glands	6	4	10
143	Gums	3	1	4
144	Floor of the Mouth	6	2	8
145	Other Parts of Mouth	10	3	13
146	Oropharynx	13	5	18
147	Nasopharynx	4	2	6
148	Hypopharynx	13	4	17
149	Pharynx Unspecified	4	1	5
150	Oesophagus	30	13	43
151	Stomach	90	48	138
152	Small Intestines	5	3	8
153	Large Intestines	238	203	441
154	Rectum and Rectosigmoid Junction	123	90	213
155	Liver and Intrahepatic Ducts	32	13	45
156	Gall Bladder and Extrahepatic Ducts	19	25	44
157	Pancreas	69	54	123
158	Peritoneum and Retroperitoneal Tissue	3	6	9
159	Digestive - N.O.S.	5	3	8
160	Nose,Nasal Cavities, Ear and Accessory	0	1	1
161	Larynx	24	6	30
162	Trachea,Bronchus and Lung	409	251	660
163-165	Other and Unspecified Respiratory Organs	9	2	11
170	Bone	6	7	13
171	Connective Tissue	9	7	16

* Unspecified tumors are not included.

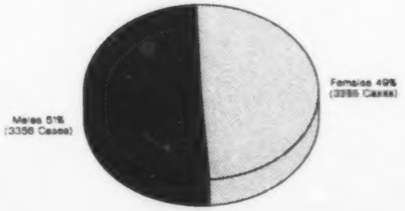
1990 TABLE XVIIb CANCER INCIDENCE - BY SITE*

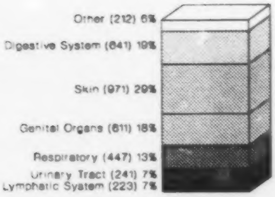
ICDA 9th Rev.	Site	Male	Female	Total
172	Malignant Melanoma of Skin	42	51	93
173	Malignant Neoplasm of Skin	927	792	1,719
174-175	Breast	3	647	650
179-182	Uterus-Corpus Except Cervix	0	519	519
180,233.1	Cervix Uteri	0	132	132
183	Ovary,Fallopian Tubes and Broad Ligaments	0	69	69
184,236.1	Other Female Genital Organs	0	12	12
185	Prostate	586	0	586
186	Testis	21	0	21
187	Other Male Genital Organs	1	0	1
188	Bladder	159	47	206
189	Other and Unspecified Urinary Organs	73	53	126
190	Eye	9	9	18
191	Brain	35	27	62
192	Other Parts of Nervous System	3	1	4
193	Thyroid Gland	11	25	36
194,164.0	Endocrine Gland	5	1	6
195-9	Other and Unspecified Sites	64	81	145
200	Lymphasarcoma and Reticulosarcoma	51	41	92
201	Hodgkins Disease	16	13	29
202	Other Lymphomas (Recticulosis)	46	37	83
203	Multiple Myeloma	35	29	64
204-8	Leukaemia	68	39	107
238.4	Polycythemia Vera	5	5	10
289.0	Myelofibrosis	2	1	3
	Total - All Sites	3,356	3,285	6,641

* Unspecified tumors are not included.

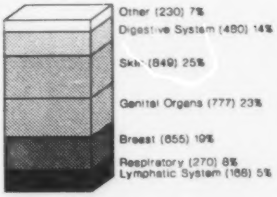
ALL SITES 1990

Incidence





Males



Females

Other (# Cases):

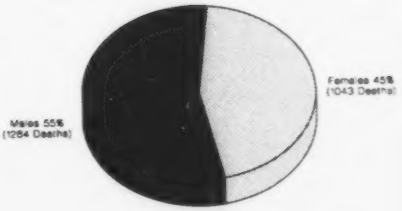
Buccal Cavity .. 126
Thyroid ... 19
Brain ... 47
Connective Tissue . 11
Bone ... 6
Breast ... 3

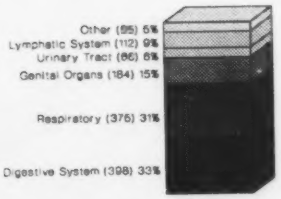
Other (# Cases):

Buccal Cavity ... 40
Thyroid ... 31
Brain ... 37
Connective Tissue ... 14
Bone ... 6
Urinary Tract ... 100

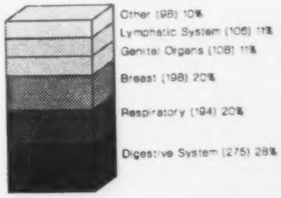
ALL SITES 1990

Mortality





Males



Females

Other (# Deaths)

Buccal Cavity .. 22
Breast ... 2
Skin .. 5
Brain ... 31
Thyroid .. 3
Bone ... 2
Connective Tissue . 6

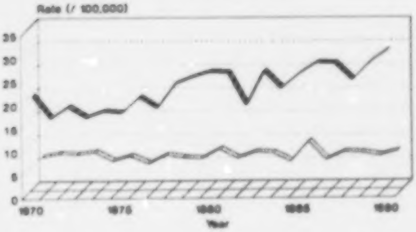
Other (# Deaths)

Buccal Cavity .. 17
Urinary Tract .. 40
Skin .. 15
Brain . 17
Thyroid .. 7
Bone .. 5
Connective Tissue .. 12

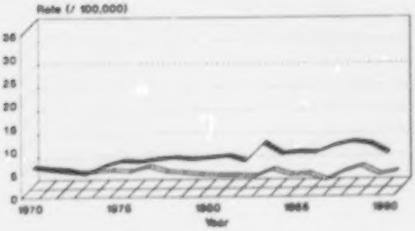
20-YEAR TRENDS

Bladder

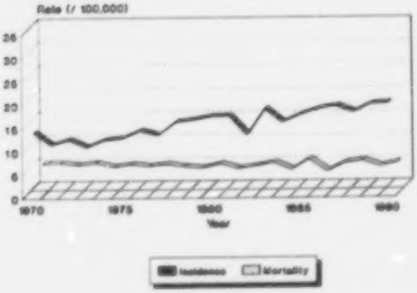
Males



Females



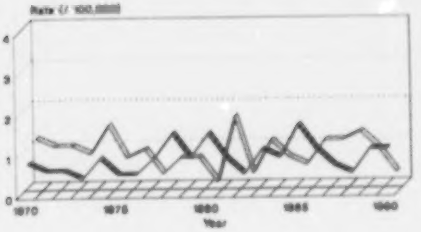
Total Population



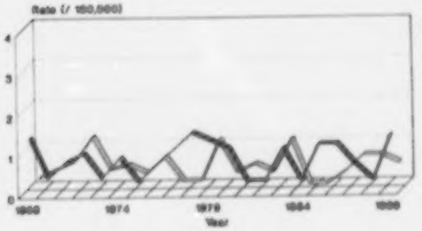
20-YEAR TRENDS

Bone

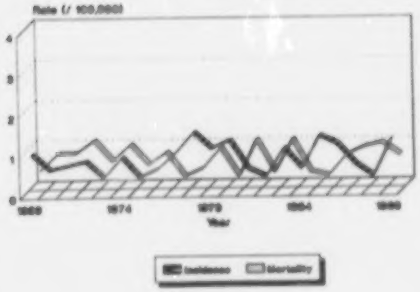
Males



Females



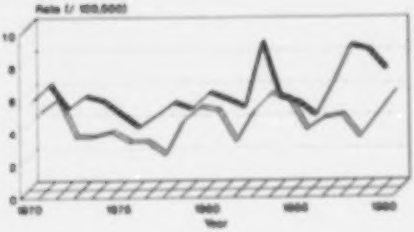
Total Population



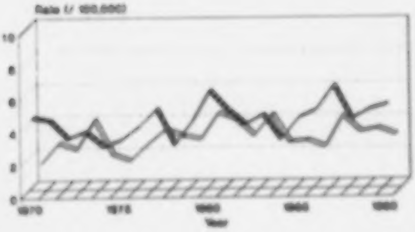
20-YEAR TRENDS

Brain

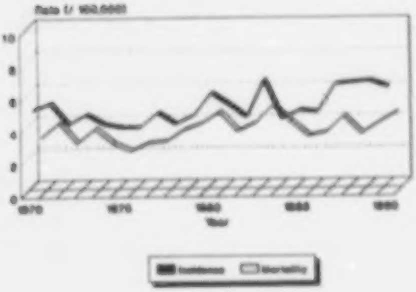
Males



Females



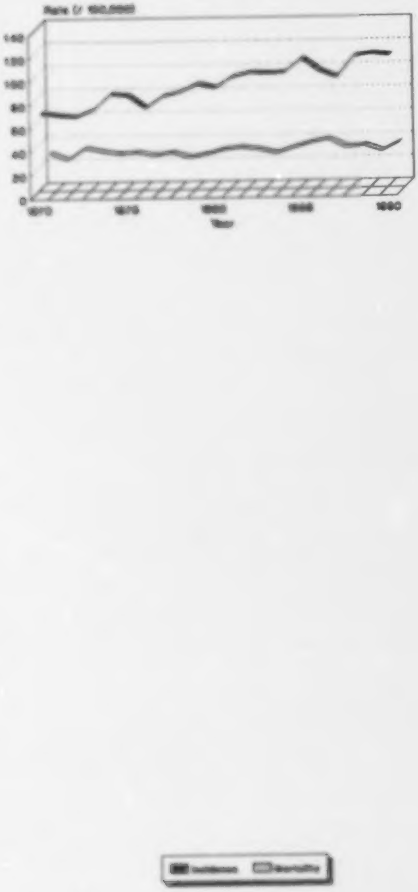
Total Population



20-YEAR TRENDS

Breast

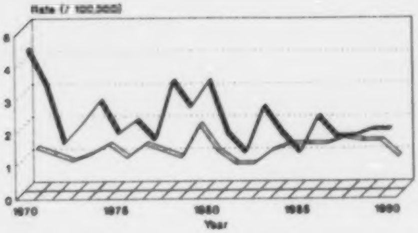
Females



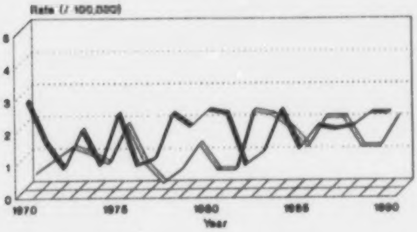
20-YEAR TRENDS

Connective Tissue

Males



Females



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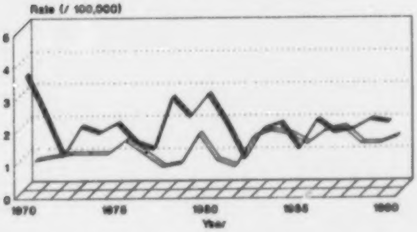
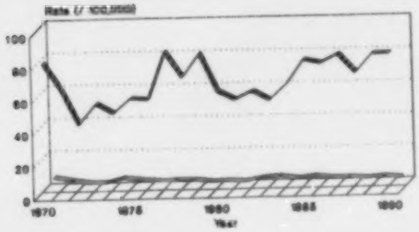


■ Incidence ☐ Mortality

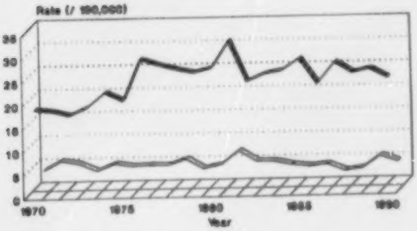
20-YEAR TRENDS

Genital Organs: Females

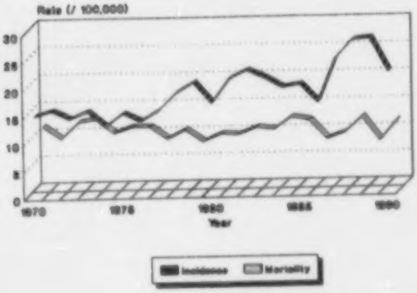
Cervix



Uterus



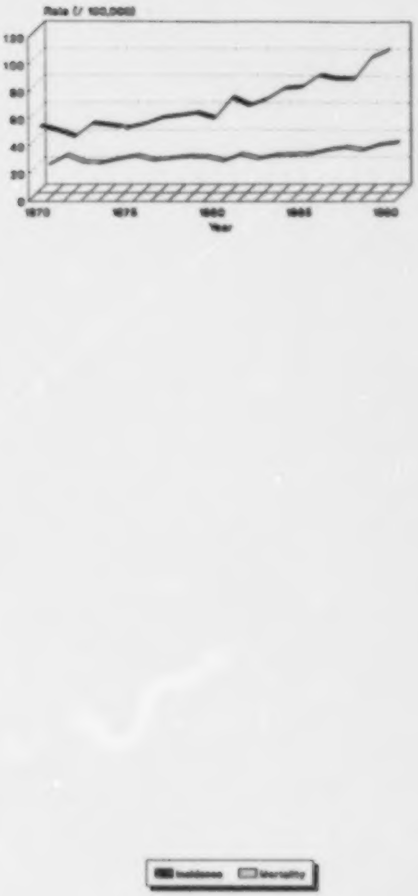
Ovary



20-YEAR TRENDS

Genital Organs: Males

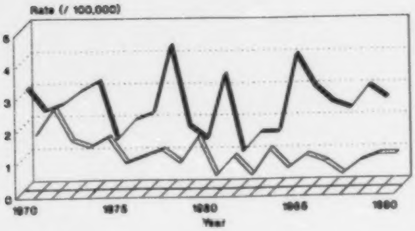
Prostate



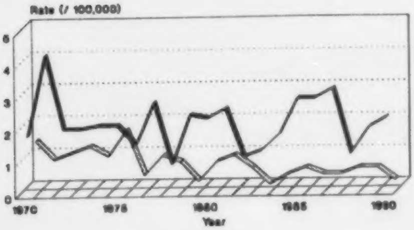
20-YEAR TRENDS

Hodgkins Disease

Males



Females



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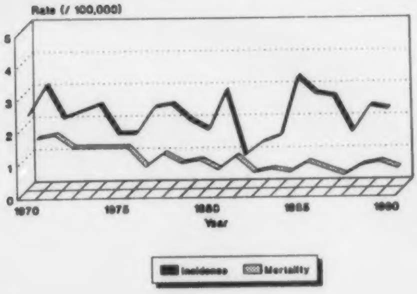
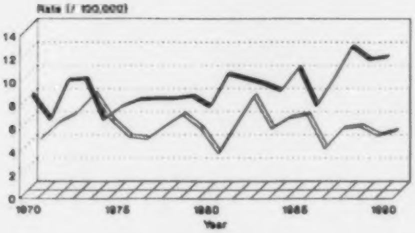


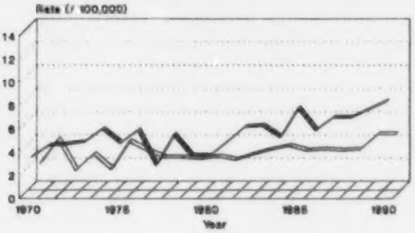
20-YEAR TRENDS

Kidney

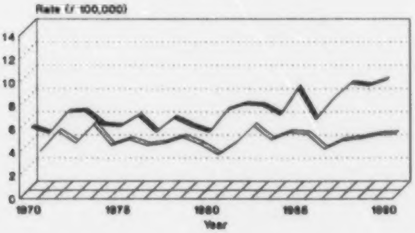
Males



Females



Total Population

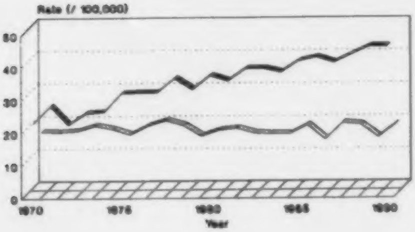


▇ Incidence ▨ Mortality

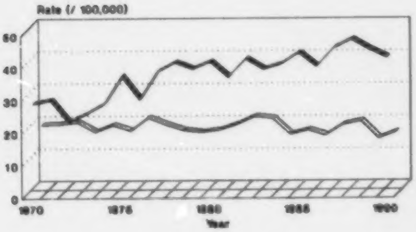
20-YEAR TRENDS

Large Bowel

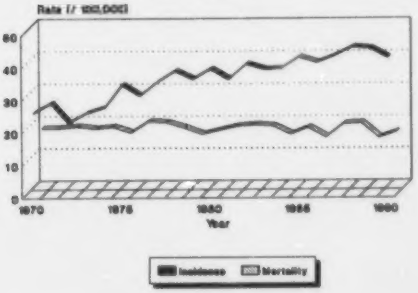
Males



Females



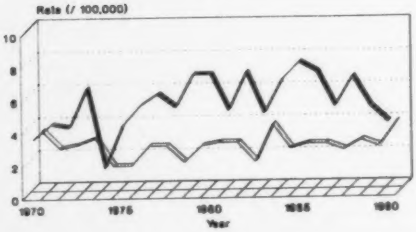
Total Population



20-YEAR TRENDS

Larynx

Males



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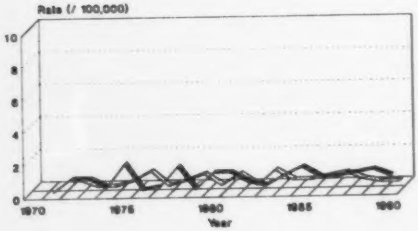

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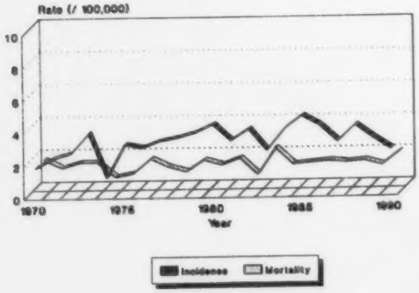
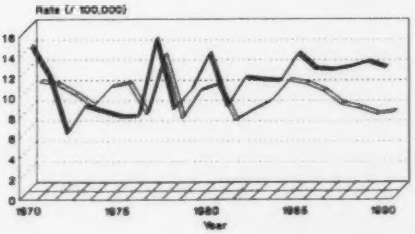


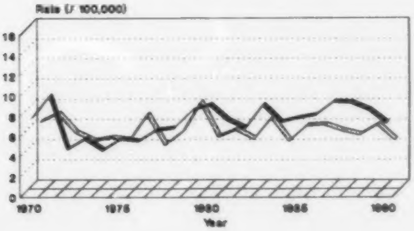
20-YEAR TRENDS

Leukaemia

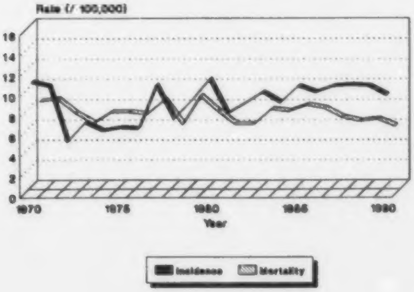
Males



Females



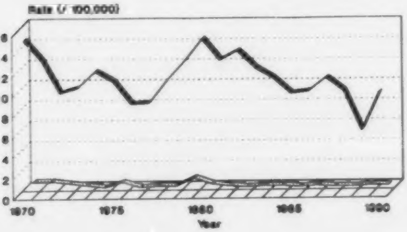
Total Population



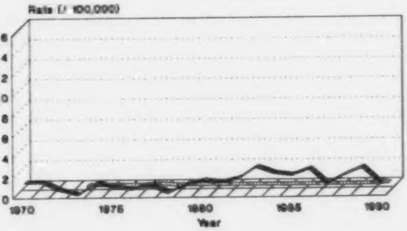
20-YEAR TRENDS

Lip

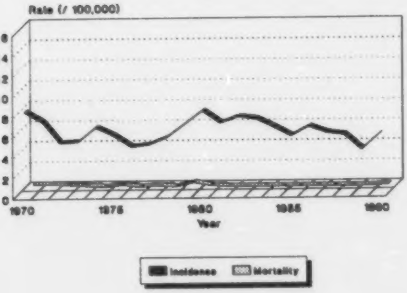
Males



Females



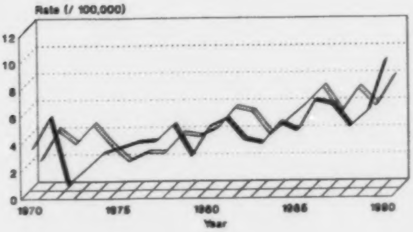
Total Population



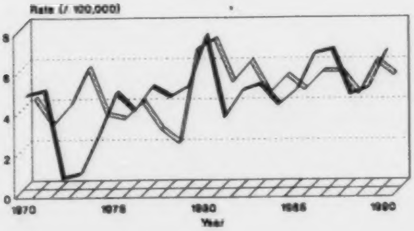
20-YEAR TRENDS

Liver

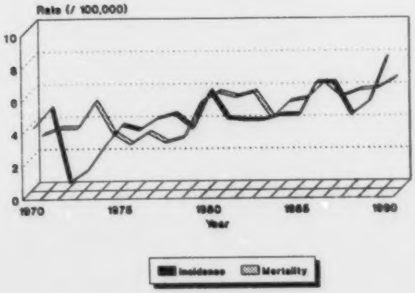
Males



Females



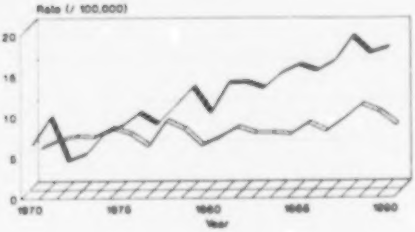
Total Population



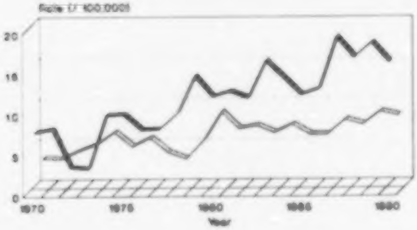
20-YEAR TRENDS

Lymphomas

Males



Females



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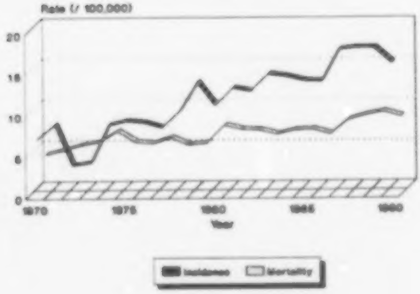
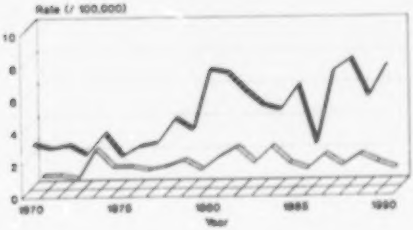


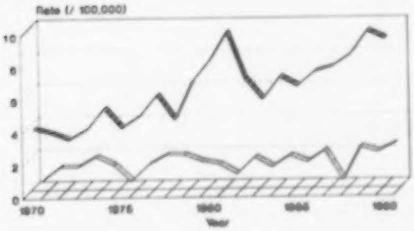
20-YEAR TRENDS

Melanoma

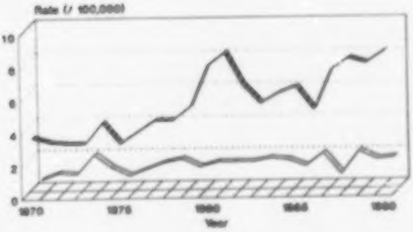
Males



Females



Total Population

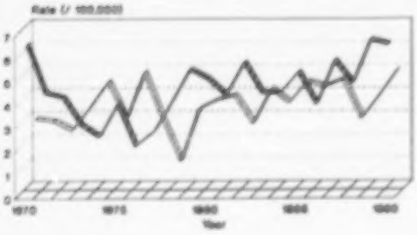


■ Incidence ▨ Mortality

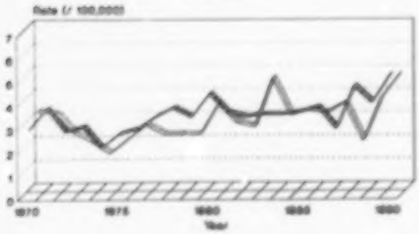
20-YEAR TRENDS

Multiple Myeloma

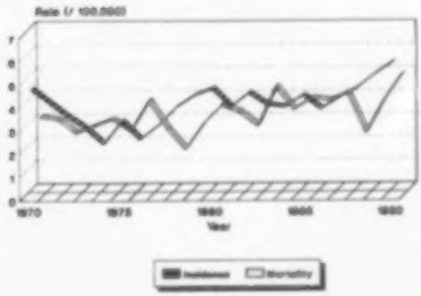
Males



Females



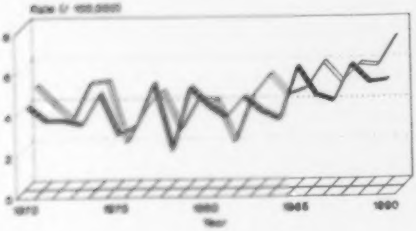
Total Population



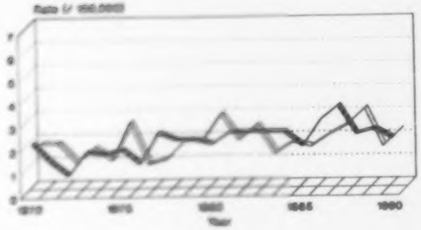
20-YEAR TRENDS

Oesophagus

Males



Females



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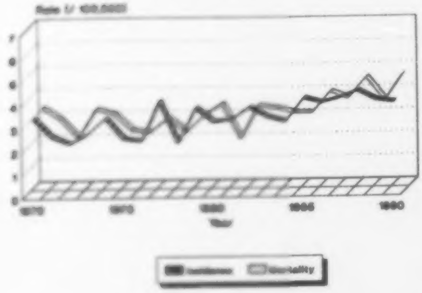
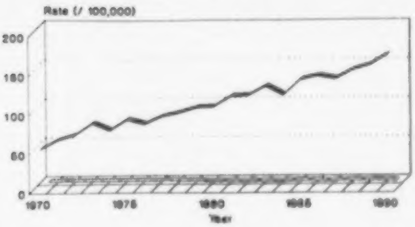


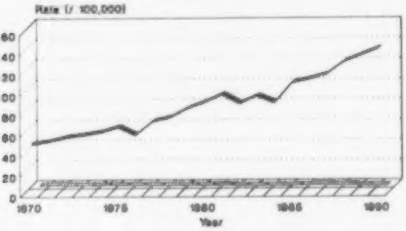
20-YEAR TRENDS

Other Malignant Neoplasms
Skin:

Males



Females



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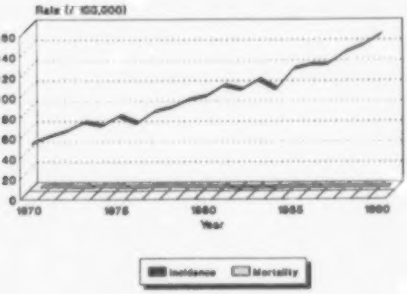
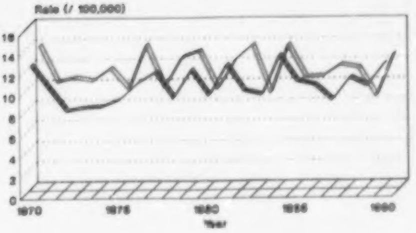


20-YEAR TRENDS

Pancreas

Males



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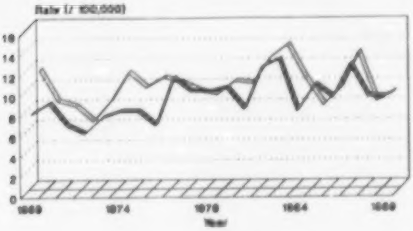

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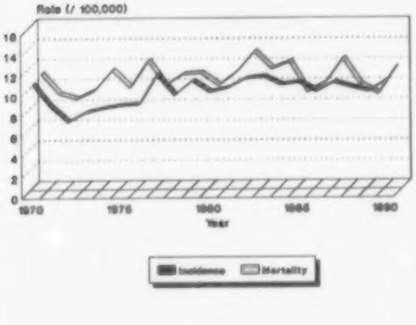
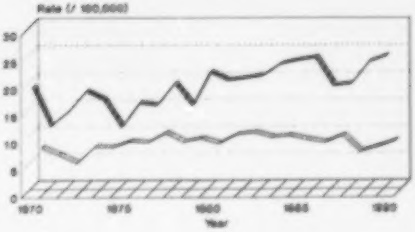


20-YEAR TRENDS

Rectum

Males



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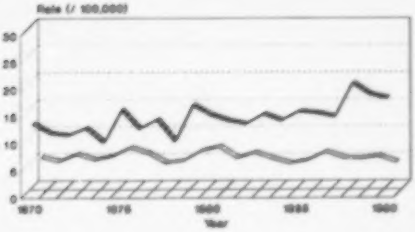

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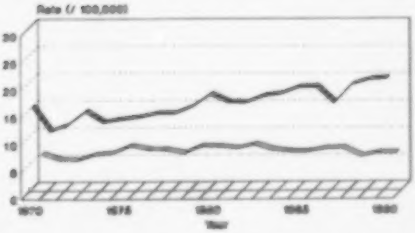
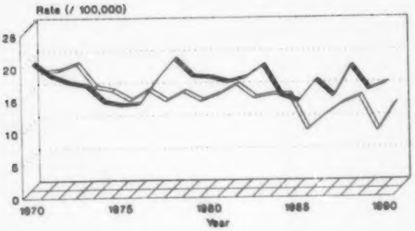


▇ Incidence ☐ Mortality

20-YEAR TRENDS

Stomach

Males



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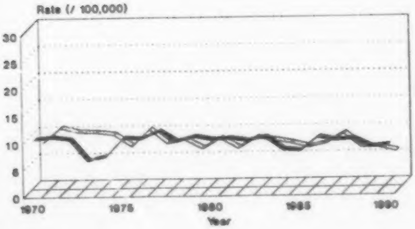

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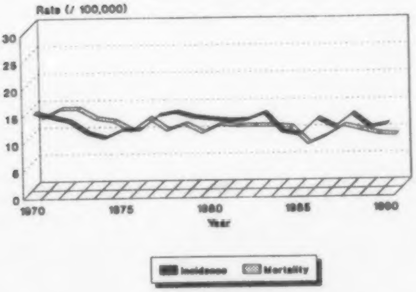
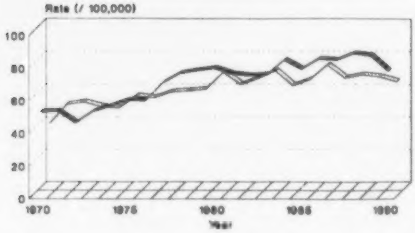


20-YEAR TRENDS

Trachea, Bronchus & Lung

Males



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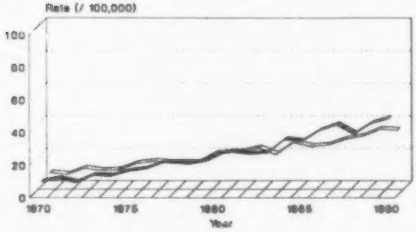
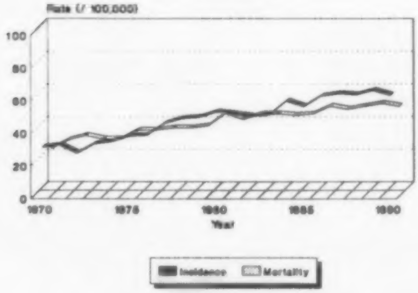


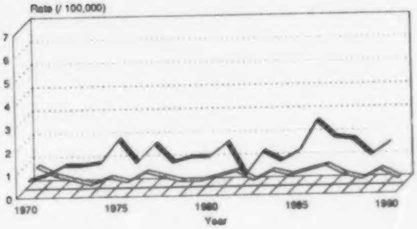
Total Population



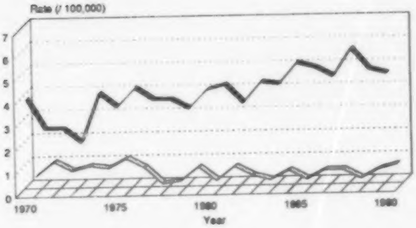
20-YEAR TRENDS

Thyroid

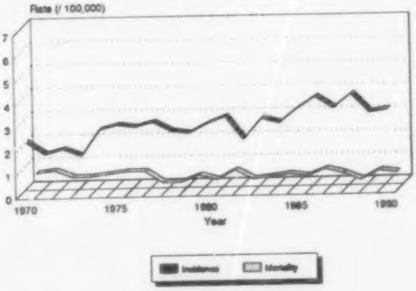
Males



Females



Total Population



RESEARCH GUIDELINES

Please communicate your needs to Director, Records and Registry, Manitoba Cancer Treatment and Research Foundation, 100 Olivia Street, Winnipeg, Manitoba, R3E 0V9. Telephone (204) 787-2197.

1. Projects must be approved by the Director, Records and Registry, with the advise of the Records and Registry Research Advisory Committee according to the following criteria:

i. The goals of the Cancer Registry.
ii. The adequacy of research design.
iii. Personnel, computer & other resource demands.
iv. Current operational demand.

2. Projects may be of three types:

i. Operational:
Necessary to the day-to-day function of the Manitoba Cancer Treatment and Research Foundation (MCTRF), eg. site reviews, radiotherapy utilization studies etc. These may be undertaken only by MCTRF staff in their fields of expertise.

ii. Research:
Open to all qualified researchers. Must be approved by the Ethics Committee, University of Manitoba. Any appropriate utilization of the resource is encouraged. In particular natural history, epidemiology and econometric studies are encouraged. Clinical studies may also be reviewed by the Protocol Review Committee of the MCTRF.

iii. Computer applications:
The computer resource is available to MCTRF personnel for analytic, process control and other applications as may be deemed feasible from time-to-time by the participants.

3. Pilot projects and feasibility studies are encouraged and may be supported by Records and Registry staff as resources permit.

4. All projects must be reviewed by the Records and Registry staff for statistical and computational feasibility prior to review by the Director. Applicants should view this process as consultive, intended to minimize effort and maximize utilization of the resource.

5. For all projects, strict confidentiality must be assured at all times. All persons accessing the Registry will be required to sign an Oath of Confidentiality.

6. While the primary objective of the Records and Registry process review is to assure efficient and proper use of the Registry and Confidentiality, research proposals which have not been externally funded and/or have not undergone independent peer review, may also be examined as to scientific merit. Clearly, projects involving extensive staff and resource commitments will be closely reviewed.

7. All projects will be prioritized by the Director. The operational requirements of the registry will always take precedence over research activity and may, from time-to-time, occupy all available resources. Staff will attempt to schedule research projects so as to minimize such inconveniences to the investigators. Prioritization guidelines will include:

i. Size of staff and computer requirements.
ii. Scientific merit as it relates to the goals of the Registry.
iii. Project deadline.
iv. Funding status of the project.

8 . Projects of type (ii) & (iii), Item 2, will be charged for resource utilization at rates to be established from time-to-time. These charges may include:

i. Statistical consultation time.
ii. Programming and programming assistance.
iii. Computer utilization time.
iv. Records and Registry staff time.
v. Consumables, telephone charges etc..

9. The data remain the property of the MCTRF, and users must acknowledge the Registry in publications and presentations.

10. Researchers who require consultation will be encouraged to use the MCTRF resource for data analysis to maximize utilization of the experience and expertise of MCTRF staff.

11. MCTRF Records and Registry will assume no responsibility for the accuracy of data reported by investigators using the Registry, or for any interpretations thereof.

12. Researchers must agree to submit to the Director all papers and reports for publication for review prior to distribution or publication to assure that the anonymity of respondents is preserved and that any reference to the Registry is factually correct.